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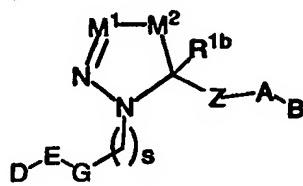
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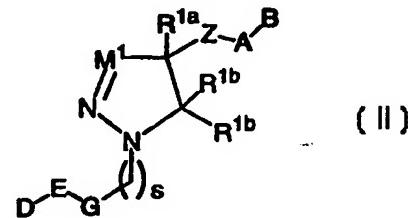
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(54) Title: DISUBSTITUTED PYRAZOLINES AND TRIAZOLINES AS FACTOR XA INHIBITORS



( I )



( II )

## (57) Abstract

The present application describes disubstituted pyrazolines and triazolines of formulae (I) and (II), or pharmaceutically acceptable salt forms thereof, wherein one of M<sup>1</sup> and M<sup>2</sup> may be N and D may be a variety of N-containing groups, which are useful as inhibitors of factor Xa.

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TITLEDISUBSTITUTED PYRAZOLINES AND TRIAZOLINES AS FACTOR XA  
INHIBITORS

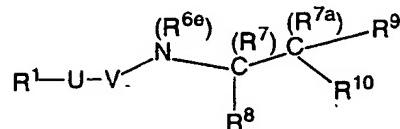
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FIELD OF THE INVENTION

This invention relates generally to disubstituted pyrazolines and triazolines which are inhibitors of trypsin-like serine protease enzymes, especially factor Xa, 10 pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

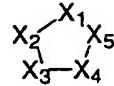
BACKGROUND OF THE INVENTION

15 WO 95/18111 addresses fibrinogen receptor antagonists, containing basic and acidic termini, of the formula:



20 wherein R<sup>1</sup> represents the basic termini, U is an alkylene or heteroatom linker, V may be a heterocycle, and the right hand portion of the molecule represents the acidic termini. The presently claimed compounds do not contain the acidic termini of WO 95/18111.

25 In U.S. Patent No. 5,463,071, Himmelsbach et al depict cell aggregation inhibitors which are 5-membered heterocycles of the formula:



30

wherein the heterocycle may be aromatic and groups A-B-C- and F-E-D- are attached to the ring system. A-B-C- can be a wide variety of substituents including a basic group attached to an aromatic ring. The F-E-D- group, however, would appear to be 35 an acidic functionality which differs from the present

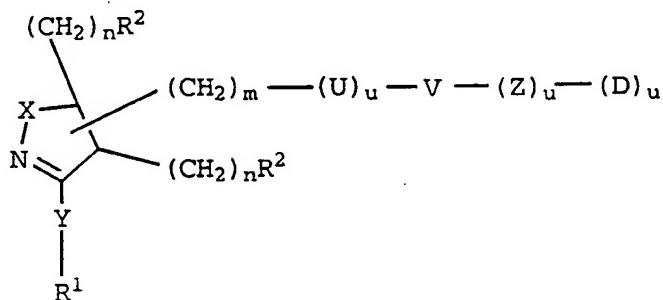
invention. Furthermore, use of these compounds as inhibitors of factor Xa is not discussed.

WO 97/47299 describes amidino and guanidino heterocyclic protease inhibitors of the formula:

5 R<sup>1</sup>-Z-X-Y-W

wherein W contains an amidino, guanidino, or imino group attached to a variety of moieties including phenyl and piperidinyl, Y is a O, N, S, or C linker or is absent; X is a heterocycle, Z is a two atom linker containing at least one heteroatom, and R<sup>1</sup> is a variety of groups including cycloalkyl, aryl, heteroaryl, and aralkyl all of which are optionally substituted. A variety of proteases are described as possible targets for these compounds including Factor Xa. The presently claimed compounds differ in that they do not contain the combination R<sup>1</sup>-Z or Y-W.

WO 97/23212 describes isoxazolines, isothiazolines, and pyrazolines of the formula:



20

wherein X is O, S or NR<sup>15</sup>. Though the pyrazolines of WO 97/23212 are indicated to be factor Xa inhibitors, they are not considered part of the present invention.

Activated factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (factor Xa, factor V,  $\text{Ca}^{2+}$  and phospholipid). Since it is calculated that one molecule of

factor Xa can generate 138 molecules of thrombin (Elodi, S., Varadi, K.: *Optimization of conditions for the catalytic effect of the factor IXa-factor VIII Complex: Probable role of the complex in the amplification of blood coagulation.*

- 5     *Thromb. Res.* **1979**, *15*, 617-629), inhibition of factor Xa may be more efficient than inactivation of thrombin in interrupting the blood coagulation system.

Therefore, efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for  
10   the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors.

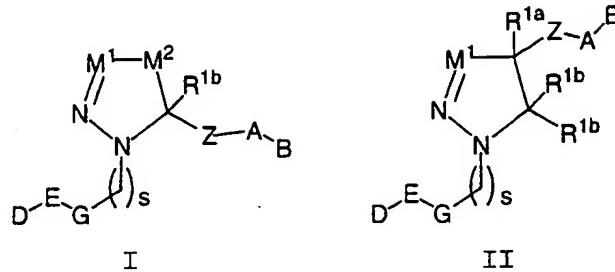
#### SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to  
15   provide novel disubstituted pyrazolines and triazolines which are useful as factor Xa inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide a method for treating thromboembolic disorders comprising  
25   administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

These and other objects, which will become apparent  
30   during the following detailed description, have been achieved by the inventors' discovery that compounds of formulae I and II:

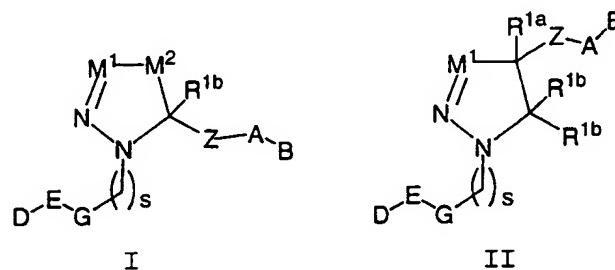


or pharmaceutically acceptable salt or prodrug forms thereof,  
wherein A, B, D, E, G, M, Z, R<sup>1a</sup>, R<sup>1b</sup>, and s are defined  
5 below, are effective factor Xa inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in a first embodiment, the present invention provides novel compounds of formulae I or II:

10



or a stereoisomer or pharmaceutically acceptable salt thereof,  
15 wherein;

M<sup>1</sup> is N or CR<sup>1c</sup>;

M<sup>2</sup> is NR<sup>1a</sup> or CR<sup>1a</sup>R<sup>1a</sup>, provided that only one of M<sup>1</sup> and M<sup>2</sup> is a  
20 N atom;

D is selected from C(=NR<sup>8</sup>)NR<sup>7</sup>R<sup>9</sup>, NHC(=NR<sup>8</sup>)NR<sup>7</sup>R<sup>9</sup>, NR<sup>8</sup>CH(=NR<sup>7</sup>),  
C(O)NR<sup>7</sup>R<sup>8</sup>, and CR<sup>8</sup>R<sup>9</sup>NR<sup>7</sup>R<sup>8</sup>;

25 E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl,  
pyridazinyl, and piperidinyl substituted with 1 R;

alternatively, D-E-G together represent pyridyl substituted  
with 1 R;

R is selected from H, Cl, F, Br, I,  $(\text{CH}_2)_t\text{OR}^3$ ,  $\text{C}_{1-4}$  alkyl,  $\text{OCF}_3$ ,  $\text{CF}_3$ ,  $\text{C}(\text{O})\text{NR}^7\text{R}^8$ , and  $(\text{CR}^8\text{R}^9)_t\text{NR}^7\text{R}^8$ ;

5 G is selected from  $\text{NHCH}_2$ ,  $\text{OCH}_2$ , and  $\text{SCH}_2$ , provided that when s is 0, then G is absent;

Z is selected from a  $\text{C}_{1-4}$  alkylene,  $(\text{CH}_2)_r\text{O}(\text{CH}_2)_r$ ,  
 $(\text{CH}_2)_r\text{NR}^3(\text{CH}_2)_r$ ,  $(\text{CH}_2)_r\text{C}(\text{O})(\text{CH}_2)_r$ ,  $(\text{CH}_2)_r\text{C}(\text{O})\text{O}(\text{CH}_2)_r$ ,  
10  $(\text{CH}_2)_r\text{OC}(\text{O})(\text{CH}_2)_r$ ,  $(\text{CH}_2)_r\text{C}(\text{O})\text{NR}^3(\text{CH}_2)_r$ ,  
 $(\text{CH}_2)_r\text{NR}^3\text{C}(\text{O})(\text{CH}_2)_r$ ,  $(\text{CH}_2)_r\text{OC}(\text{O})\text{O}(\text{CH}_2)_r$ ,  
 $(\text{CH}_2)_r\text{OC}(\text{O})\text{NR}^3(\text{CH}_2)_r$ ,  $(\text{CH}_2)_r\text{NR}^3\text{C}(\text{O})\text{O}(\text{CH}_2)_r$ ,  
 $(\text{CH}_2)_r\text{NR}^3\text{C}(\text{O})\text{NR}^3(\text{CH}_2)_r$ ,  $(\text{CH}_2)_r\text{S}(\text{O})_p(\text{CH}_2)_r$ ,  
 $(\text{CH}_2)_r\text{SO}_2\text{NR}^3(\text{CH}_2)_r$ ,  $(\text{CH}_2)_r\text{NR}^3\text{SO}_2(\text{CH}_2)_r$ , and  
15  $(\text{CH}_2)_r\text{NR}^3\text{SO}_2\text{NR}^3(\text{CH}_2)_r$ , provided that Z does not form a N-  
N, N-O, N-S,  $\text{NCH}_2\text{N}$ ,  $\text{NCH}_2\text{O}$ , or  $\text{NCH}_2\text{S}$  bond with group A;

$\text{R}^{1a}$  and  $\text{R}^{1b}$  are, at each occurrence, independently selected from H,  $-(\text{CH}_2)_r\text{R}^{1''}$ ,  $\text{NCH}_2\text{R}^{1''}$ ,  $\text{OCH}_2\text{R}^{1''}$ ,  $\text{SCH}_2\text{R}^{1''}$ ,  
20  $\text{N}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1''}$ ,  $\text{O}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1''}$ , and  $\text{S}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1''}$ ;

$\text{R}^{1c}$  is selected from H,  $-(\text{CH}_2)_q\text{R}^{1''}$ ,  $\text{C}_{1-3}$  alkyl,  $\text{C}(\text{O})\text{R}^{2c}$ ,  
 $(\text{CF}_2)_r\text{CO}_2\text{R}^{2c}$ ,  $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$ ,  $\text{C}_{3-6}$  carbocyclic residue substituted with 0-2 R<sup>4</sup>, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R<sup>4</sup>;  
25

$\text{R}^{1'}$  is selected from H,  $\text{C}_{1-3}$  alkyl, halo,  $(\text{CF}_2)_r\text{CF}_3$ ,  $\text{OR}^2$ ,  $\text{NR}^2\text{R}^{2a}$ ,  $\text{C}(\text{O})\text{R}^{2c}$ ,  $\text{OC}(\text{O})\text{R}^2$ ,  $(\text{CF}_2)_r\text{CO}_2\text{R}^{2c}$ ,  $\text{S}(\text{O})_p\text{R}^{2b}$ ,  
30  $\text{NR}^2(\text{CH}_2)_r\text{OR}^2$ ,  $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$ ,  $\text{NR}^2\text{C}(\text{O})\text{NHR}^{2b}$ ,  $\text{NR}^2\text{C}(\text{O})_2\text{R}^{2a}$ ,  $\text{OC}(\text{O})\text{NR}^{2b}$ ,  $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$ ,  $\text{SO}_2\text{NR}^2\text{R}^{2a}$ ,  $\text{NR}^2\text{SO}_2\text{R}^{2b}$ ,  $\text{C}_{3-6}$  carbocyclic residue substituted with 0-2 R<sup>4</sup>, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R<sup>4</sup>;  
35

$\text{R}^{1''}$  is selected from H,  $\text{C}(\text{O})\text{R}^{2b}$ ,  $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$ ,  $\text{S}(\text{O})\text{R}^{2b}$ ,  $\text{S}(\text{O})_2\text{R}^{2b}$ , and  $\text{SO}_2\text{NR}^2\text{R}^{2a}$ ;

- R<sup>2</sup>, at each occurrence, is selected from H, CF<sub>3</sub>, C<sub>1-6</sub> alkyl, benzyl, C<sub>3-6</sub> carbocyclic residue substituted with 0-2 R<sup>4b</sup>, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R<sup>4b</sup>;
- 5
- R<sup>2a</sup>, at each occurrence, is selected from H, CF<sub>3</sub>, C<sub>1-6</sub> alkyl, benzyl, C<sub>3-6</sub> carbocyclic residue substituted with 0-2 R<sup>4b</sup>, and 5-6 membered heterocyclic system containing from 10 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R<sup>4b</sup>;
- R<sup>2b</sup>, at each occurrence, is selected from CF<sub>3</sub>, C<sub>1-4</sub> alkoxy, C<sub>1-6</sub> alkyl, benzyl, C<sub>3-6</sub> carbocyclic residue substituted with 0-2 R<sup>4b</sup>, and 5-6 membered heterocyclic system containing from 15 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R<sup>4b</sup>;
- 20 R<sup>2c</sup>, at each occurrence, is selected from CF<sub>3</sub>, OH, C<sub>1-4</sub> alkoxy, C<sub>1-6</sub> alkyl, benzyl, C<sub>3-6</sub> carbocyclic residue substituted with 0-2 R<sup>4b</sup>, and 5-6 membered heterocyclic system containing from 25 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R<sup>4b</sup>;
- alternatively, R<sup>2</sup> and R<sup>2a</sup> combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R<sup>4b</sup> which contains from 30 0-1 additional heteroatoms selected from the group consisting of N, O, and S;
- R<sup>3</sup>, at each occurrence, is selected from H, C<sub>1-4</sub> alkyl, and phenyl;
- 35 R<sup>3a</sup>, at each occurrence, is selected from H, C<sub>1-4</sub> alkyl, and phenyl;

A is selected from:

$C_{3-10}$  carbocyclic residue substituted with 0-2  $R^4$ , and  
5-10 membered heterocyclic system containing from 1-4  
heteroatoms selected from the group consisting of N, O, and S  
substituted with 0-2  $R^4$ ;

5

B is selected from:

$X-Y$ ,  $NR^2R^{2a}$ ,  $C(=NR^2)NR^2R^{2a}$ ,  $NR^2C(=NR^2)NR^2R^{2a}$ ,

$C_{3-10}$  carbocyclic residue substituted with 0-2  $R^{4a}$ , and

5-10 membered heterocyclic system containing from 1-4

10 heteroatoms selected from the group consisting of N, O, and S  
substituted with 0-2  $R^{4a}$ ;

$X$  is selected from  $C_{1-4}$  alkylene,  $-CR^2(CR^2R^{2b})(CH_2)_t-$ ,  $-C(O)-$ ,

$-C(=NR)-$ ,  $-CR^2(NR^{1''}R^2)-$ ,  $-CR^2(OR^2)-$ ,  $-CR^2(SR^2)-$ ,

15  $-C(O)CR^2R^{2a}-$ ,  $-CR^2R^{2a}C(O)$ ,  $-S(O)_p-$ ,  $-S(O)_pCR^2R^{2a}-$ ,

$-CR^2R^{2a}S(O)_p-$ ,  $-S(O)_2NR^2-$ ,  $-NR^2S(O)_2-$ ,  $-NR^2S(O)_2CR^2R^{2a}-$ ,

$-CR^2R^{2a}S(O)_2NR^2-$ ,  $-NR^2S(O)_2NR^2-$ ,  $-C(O)NR^2-$ ,  $-NR^2C(O)-$ ,

$-C(O)NR^2CR^2R^{2a}-$ ,  $-NR^2C(O)CR^2R^{2a}-$ ,  $-CR^2R^{2a}C(O)NR^2-$ ,

$-CR^2R^{2a}NR^2C(O)-$ ,  $-NR^2C(O)O-$ ,  $-OC(O)NR^2-$ ,  $-NR^2C(O)NR^2-$ ,

20  $-NR^2-$ ,  $-NR^2CR^2R^{2a}-$ ,  $-CR^2R^{2a}NR^2-$ ,  $O$ ,  $-CR^2R^{2a}O-$ , and  
 $-OCR^2R^{2a}-$ ;

Y is selected from:

$(CH_2)_rNR^2R^{2a}$ , provided that X-Y do not form a N-N, O-N,

25 or S-N bond,

$C_{3-10}$  carbocyclic residue substituted with 0-2  $R^{4a}$ , and

5-10 membered heterocyclic system containing from 1-4

heteroatoms selected from the group consisting of N, O, and S  
substituted with 0-2  $R^{4a}$ ;

30

$R^4$ , at each occurrence, is selected from =O,  $(CH_2)_rOR^2$ , halo,

$C_{1-4}$  alkyl, -CN,  $NO_2$ ,  $(CH_2)_rNR^2R^{2a}$ ,  $(CH_2)_rC(O)R^{2b}$ ,

$NR^2C(O)R^{2b}$ ,  $C(O)NR^2R^{2a}$ ,  $NR^2C(O)NR^2R^{2a}$ ,  $CH(=NR^2)NR^2R^{2a}$ ,

$NHC(=NR^2)NR^2R^{2a}$ ,  $SO_2NR^2R^{2a}$ ,  $NR^2SO_2NR^2R^{2a}$ ,  $NR^2SO_2-C_{1-4}$

35 alkyl,  $NR^2SO_2R^5$ ,  $S(O)_pR^5$ ,  $(CF_2)_rCF_3$ ,  $NCH_2R^{1''}$ ,  $OCH_2R^{1''}$ ,  
 $SCH_2R^{1''}$ ,  $N(CH_2)_2(CH_2)_tR^{1'}$ ,  $O(CH_2)_2(CH_2)_tR^{1'}$ , and  
 $S(CH_2)_2(CH_2)_tR^{1'}$ ,

alternatively, one R<sup>4</sup> is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

5 R<sup>4a</sup>, at each occurrence, is selected from =O, (CH<sub>2</sub>)<sub>r</sub>OR<sup>2</sup>, halo, C<sub>1-4</sub> alkyl, -CN, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, (CH<sub>2</sub>)<sub>r</sub>C(O)R<sup>2b</sup>, NR<sup>2</sup>C(O)R<sup>2b</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>C(O)NR<sup>2</sup>R<sup>2a</sup>, CH(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>, NHC(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>SO<sub>2</sub>-C<sub>1-4</sub> alkyl, NR<sup>2</sup>SO<sub>2</sub>R<sup>5</sup>, S(O)<sub>p</sub>R<sup>5</sup>, and (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>;

10 alternatively, one R<sup>4a</sup> is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-1 R<sup>5</sup>;

15 R<sup>4b</sup>, at each occurrence, is selected from =O, (CH<sub>2</sub>)<sub>r</sub>OR<sup>3</sup>, halo, C<sub>1-4</sub> alkyl, -CN, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>r</sub>NR<sup>3</sup>R<sup>3a</sup>, (CH<sub>2</sub>)<sub>r</sub>C(O)R<sup>3</sup>, NR<sup>3</sup>C(O)R<sup>3a</sup>, C(O)NR<sup>3</sup>R<sup>3a</sup>, NR<sup>3</sup>C(O)NR<sup>3</sup>R<sup>3a</sup>, CH(=NR<sup>3</sup>)NR<sup>3</sup>R<sup>3a</sup>, NH<sup>3</sup>C(=NR<sup>3</sup>)NR<sup>3</sup>R<sup>3a</sup>, SO<sub>2</sub>NR<sup>3</sup>R<sup>3a</sup>, NR<sup>3</sup>SO<sub>2</sub>NR<sup>3</sup>R<sup>3a</sup>, NR<sup>3</sup>SO<sub>2</sub>-C<sub>1-4</sub> alkyl, NR<sup>3</sup>SO<sub>2</sub>CF<sub>3</sub>, NR<sup>3</sup>SO<sub>2</sub>-phenyl, S(O)<sub>p</sub>CF<sub>3</sub>, S(O)<sub>p</sub>-C<sub>1-4</sub> alkyl, S(O)<sub>p</sub>-phenyl, and (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>;

25 R<sup>5</sup>, at each occurrence, is selected from CF<sub>3</sub>, C<sub>1-6</sub> alkyl, phenyl substituted with 0-2 R<sup>6</sup>, and benzyl substituted with 0-2 R<sup>6</sup>;

25 R<sup>6</sup>, at each occurrence, is selected from H, OH, (CH<sub>2</sub>)<sub>r</sub>OR<sup>2</sup>, halo, C<sub>1-4</sub> alkyl, CN, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, (CH<sub>2</sub>)<sub>r</sub>C(O)R<sup>2b</sup>, NR<sup>2</sup>C(O)R<sup>2b</sup>, NR<sup>2</sup>C(O)NR<sup>2</sup>R<sup>2a</sup>, CH(=NH)NH<sub>2</sub>, NHC(=NH)NH<sub>2</sub>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, and NR<sup>2</sup>SO<sub>2</sub>C<sub>1-4</sub> alkyl;

30 R<sup>7</sup>, at each occurrence, is selected from H, OH, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy, C<sub>1-4</sub> alkoxy carbonyl, (CH<sub>2</sub>)<sub>n</sub>-phenyl, C<sub>6-10</sub> aryloxy, C<sub>6-10</sub> aryloxycarbonyl, C<sub>6-10</sub> arylmethylcarbonyl, C<sub>1-4</sub> alkylcarbonyloxy C<sub>1-4</sub> alkoxy carbonyl, C<sub>6-10</sub> arylcarbonyloxy C<sub>1-4</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C<sub>1-4</sub> alkoxy carbonyl;

R<sup>8</sup>, at each occurrence, is selected from H, C<sub>1-6</sub> alkyl and (CH<sub>2</sub>)<sub>n</sub>-phenyl;

alternatively, R<sup>7</sup> and R<sup>8</sup> combine to form a 5 or 6 membered  
5 saturated, ring which contains from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R<sup>9</sup>, at each occurrence, is selected from H, C<sub>1-6</sub> alkyl and (CH<sub>2</sub>)<sub>n</sub>-phenyl;

n, at each occurrence, is selected from 0, 1, 2, and 3;

m, at each occurrence, is selected from 0, 1, and 2;

15 p, at each occurrence, is selected from 0, 1, and 2;

q, at each occurrence is selected from 1 and 2;

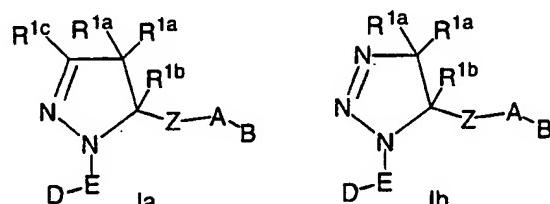
20 r, at each occurrence, is selected from 0, 1, 2, and 3;

s, at each occurrence, is selected from 0, 1, and 2; and,

t, at each occurrence, is selected from 0 and 1.

25

[2] In a preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib:



30

wherein;

Z is selected from a CH<sub>2</sub>O, OCH<sub>2</sub>, CH<sub>2</sub>NH, NHCH<sub>2</sub>, C(O), CH<sub>2</sub>C(O), C(O)CH<sub>2</sub>, NHC(O), C(O)NH, CH<sub>2</sub>S(O)<sub>2</sub>, S(O)<sub>2</sub>(CH<sub>2</sub>), SO<sub>2</sub>NH, and NHSO<sub>2</sub>, provided that Z does not form a N-N, N-O, NCH<sub>2</sub>N, or NCH<sub>2</sub>O bond with group A;

5

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R<sup>4</sup>; phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl,

10 pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

20

B is selected from: Y, X-Y, NR<sup>2</sup>R<sup>2a</sup>, C(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>, and NR<sup>2</sup>C(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>;

25

X is selected from C<sub>1-4</sub> alkylene, -C(O)-, -C(=NR)-, -CR<sup>2</sup>(NR<sup>2</sup>R<sup>2a</sup>)-, -C(O)CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>C(O)-, -C(O)NR<sup>2</sup>-, -NR<sup>2</sup>C(O)-, -C(O)NR<sup>2</sup>CR<sup>2</sup>R<sup>2a</sup>-, -NR<sup>2</sup>C(O)CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>C(O)NR<sup>2</sup>-, -CR<sup>2</sup>R<sup>2a</sup>NR<sup>2</sup>C(O)-, -NR<sup>2</sup>C(O)NR<sup>2</sup>-, -NR<sup>2</sup>- , -NR<sup>2</sup>CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>NR<sup>2</sup>-, O, -CR<sup>2</sup>R<sup>2a</sup>O-, and -OCR<sup>2</sup>R<sup>2a</sup>-;

30

Y is NR<sup>2</sup>R<sup>2a</sup>, provided that X-Y do not form a N-N or O-N bond;

alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R<sup>4a</sup>;

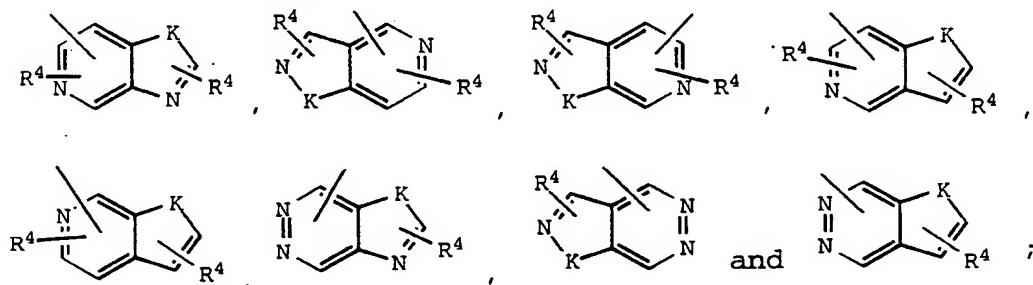
35

cyclopropyl, cyclopentyl, cyclohexyl, phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl,

isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl,  
 thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,  
 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,  
 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl,  
 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl,  
 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl,  
 benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl,  
 benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl,  
 benzisothiazolyl, and isoindazolyl;

10

alternatively, Y is selected from the following bicyclic  
 heteroaryl ring systems:



15

K is selected from O, S, NH, and N.

[3] In a more preferred embodiment, the present invention  
 20 provides novel compounds of formulae Ia-Ib, wherein;

Z is selected from a C(O), CH<sub>2</sub>C(O), C(O)CH<sub>2</sub>, NHC(O), C(O)NH,  
 C(O)N(CH<sub>3</sub>), CH<sub>2</sub>S(O)<sub>2</sub>, S(O)<sub>2</sub>(CH<sub>2</sub>), SO<sub>2</sub>NH, and NHSO<sub>2</sub>,  
 provided that Z does not form a N-N or NCH<sub>2</sub>N bond with  
 25 group A.

[4] In an even more preferred embodiment, the present  
 invention provides novel compounds of formulae Ia-Ib, wherein;

30

E is phenyl substituted with R or 2-pyridyl substituted with  
 R;

D is selected from C(O)NH<sub>2</sub>, C(=NH)NH<sub>2</sub>, CH<sub>2</sub>NH<sub>2</sub>, CH<sub>2</sub>NHCH<sub>3</sub>, CH(CH<sub>3</sub>)NH<sub>2</sub>, and C(CH<sub>3</sub>)<sub>2</sub>NH<sub>2</sub>; and,

5 R is selected from H, OCH<sub>3</sub>, Cl, and F.

[5] In a further preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib, wherein;

10 D-E is selected from 3-amidinophenyl, 3-aminomethylphenyl, 3-aminocarbonylphenyl, 3-(methylaminomethyl)phenyl, 3-(1-aminoethyl)phenyl, 3-(2-amino-2-propyl)phenyl, 4-chloro-3-amidinophenyl, 4-chloro-3-aminomethylphenyl, 4-chloro-15 3-(methylaminomethyl)phenyl, 4-fluoro-3-amidinophenyl, 4-fluoro-3-aminomethylphenyl, 4-fluoro-3-(methylaminomethyl)phenyl, 6-amidinopyrid-2-yl, 6-aminomethylpyrid-2-yl, 6-aminocarbonylpyrid-2-yl, 6-(methylaminomethyl)pyrid-2-yl, 6-(1-aminoethyl)pyrid-2-20 yl, and 6-(2-amino-2-propyl)pyrid-2-yl.

[6] In another even more preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib, wherein;

25 Z is C(O)CH<sub>2</sub> and CONH, provided that Z does not form a N-N bond with group A;

30 A is selected from phenyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R<sup>4</sup>; and,

B is selected from X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, and imidazolyl, and is substituted with 0-1 R<sup>4a</sup>;

35 R<sup>4</sup>, at each occurrence, is selected from OH, (CH<sub>2</sub>)<sub>r</sub>OR<sup>2</sup>, halo, C<sub>1-4</sub> alkyl, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, and (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>;

R<sup>4a</sup> is selected from C<sub>1-4</sub> alkyl, CF<sub>3</sub>, S(O)<sub>p</sub>R<sup>5</sup>, SO<sub>2</sub>NR<sup>2a</sup>, and 1-CF<sub>3</sub>-tetrazol-2-yl;

R<sup>5</sup>, at each occurrence, is selected from CF<sub>3</sub>, C<sub>1-6</sub> alkyl,  
5 phenyl, and benzyl;

X is CH<sub>2</sub> or C(O); and,

Y is selected from pyrrolidino and morpholino.

10

[7] In another further preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib, wherein;

15 A is selected from the group: phenyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,

20 B is selected from the group: 2-CF<sub>3</sub>-phenyl, 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 2-(dimethylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 4-morpholino, 2-(1'-CF<sub>3</sub>-tetrazol-2-yl)phenyl, 4-morpholinocarbonyl, 2-methyl-1-imidazolyl, 25 5-methyl-1-imidazolyl, 2-methylsulfonyl-1-imidazolyl and, 5-methyl-1,2,3-triazolyl.

30 [8] In another even more preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib, wherein;

E is phenyl substituted with R or 2-pyridyl substituted with R;

35 D is selected from C(O)NH<sub>2</sub>, C(=NH)NH<sub>2</sub>, CH<sub>2</sub>NH<sub>2</sub>, CH<sub>2</sub>NHCH<sub>3</sub>, CH(CH<sub>3</sub>)NH<sub>2</sub>, and C(CH<sub>3</sub>)<sub>2</sub>NH<sub>2</sub>; and,

R is selected from H, OCH<sub>3</sub>, Cl, and F;

Z is C(O)CH<sub>2</sub> and CONH, provided that Z does not form a N-N bond with group A;

5 A is selected from phenyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R<sup>4</sup>; and,

B is selected from X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, and imidazolyl, and is substituted with  
10 0-1 R<sup>4a</sup>;

R<sup>4</sup>, at each occurrence, is selected from OH, (CH<sub>2</sub>)<sub>r</sub>OR<sup>2</sup>, halo, C<sub>1-4</sub> alkyl, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, and (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>;

15 R<sup>4a</sup> is selected from C<sub>1-4</sub> alkyl, CF<sub>3</sub>, S(O)<sub>p</sub>R<sup>5</sup>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, and 1-CF<sub>3</sub>-tetrazol-2-yl;

R<sup>5</sup>, at each occurrence, is selected from CF<sub>3</sub>, C<sub>1-6</sub> alkyl, phenyl, and benzyl;

20 X is CH<sub>2</sub> or C(O); and,

Y is selected from pyrrolidino and morpholino.

25

[9] In another further preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib, wherein;

D-E is selected from 3-amidinophenyl, 3-aminomethylphenyl, 3-30 aminocarbonylphenyl, 3-(methylaminomethyl)phenyl, 3-(1-aminoethyl)phenyl, 3-(2-amino-2-propyl)phenyl, 4-chloro-3-amidinophenyl, 4-chloro-3-aminomethylphenyl, 4-chloro-3-(methylaminomethyl)phenyl, 4-fluoro-3-amidinophenyl, 4-fluoro-3-aminomethylphenyl, 4-fluoro-3-(methylaminomethyl)phenyl, 6-amidinopyrid-2-yl, 6-aminomethylpyrid-2-yl, 6'-aminocarbonylpyrid-2-yl, 6-(methylaminomethyl)pyrid-2-yl, 6-(1-aminoethyl)pyrid-2-yl, 6-(2-amino-2-propyl)pyrid-2-yl;

A is selected from the group: phenyl, 2-pyridyl, 3-pyridyl,  
2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-  
phenyl, 2-methylphenyl, 2-aminophenyl, and 2-  
methoxyphenyl; and,

5

B is selected from the group: 2-CF<sub>3</sub>-phenyl, 2-  
(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 2-  
(dimethylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-  
10 (methylsulfonyl)phenyl, 4-morpholino, 2-(1'-CF<sub>3</sub>-tetrazol-  
2-yl)phenyl, 4-morpholinocarbonyl, 2-methyl-1-imidazolyl,  
5-methyl-1-imidazolyl, 2-methylsulfonyl-1-imidazolyl and,  
5-methyl-1,2,3-triazolyl.

10

15

[10] In a still further preferred embodiment, the present invention provides a novel compound of formula Ia.

20

[11] In another still further preferred embodiment, the present invention provides a novel compound of formula Ib.

25

[12] In another even more preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib, wherein;

D is selected from C(=NR<sup>8</sup>)NR<sup>7</sup>R<sup>9</sup>, C(O)NR<sup>7</sup>R<sup>8</sup>, NR<sup>7</sup>R<sup>8</sup>, and  
CH<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>;

30

E is phenyl substituted with R or pyridyl substituted with R;

R is selected from H, Cl, F, OR<sup>3</sup>, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, OCF<sub>3</sub>, and CF<sub>3</sub>;

35

Z is selected from C(O), CH<sub>2</sub>C(O), C(O)CH<sub>2</sub>, NHC(O), and C(O)NH,  
provided that Z does not form a N-N bond with group A;

$R^{1a}$  and  $R^{1b}$  are, at each occurrence, independently selected from H,  $-(CH_2)_rR^{1'}$ ,  $NCH_2R^{1''}$ ,  $OCH_2R^{1''}$ ,  $SCH_2R^{1''}$ ,  $N(CH_2)_2(CH_2)_tR^{1'}$ ,  $O(CH_2)_2(CH_2)_tR^{1'}$ , and  $S(CH_2)_2(CH_2)_tR^{1'}$ ;

5  $R^{1c}$  is selected from H,  $-(CH_2)_qR^{1'}$ ,  $C_{1-3}$  alkyl,  $C(O)R^{2c}$ ,  $(CF_2)_rCO_2R^{2c}$ , and  $C(O)NR^{2a}$ ;

$R^{1'}$ , at each occurrence, is selected from H,  $C_{1-3}$  alkyl, halo,  $(CF_2)_rCF_3$ ,  $OR^2$ ,  $NR^2R^{2a}$ ,  $C(O)R^{2c}$ ,  $(CF_2)_rCO_2R^{2c}$ ,  $S(O)_pR^{2b}$ ,  
10  $NR^2(CH_2)_rOR^2$ ,  $NR^2C(O)R^{2b}$ ,  $NR^2C(O)_2R^{2b}$ ,  $C(O)NR^2R^{2a}$ ,  $SO_2NR^2R^{2a}$ , and  $NR^2SO_2R^{2b}$ ;

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2  $R^4$ ;  
15 phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, and imidazolyl;

20 B is selected from: Y, X-Y,  $NR^2R^{2a}$ ,  $C(=NR^2)NR^2R^{2a}$ , and  $NR^2C(=NR^2)NR^2R^{2a}$ ;

X is selected from  $CH_2$ ,  $-CR^2(CR^2R^{2b})(CH_2)_t-$ ,  $-C(O)-$ ,  $-C(=NR)-$ ,  $-CH(NR^2R^{2a})-$ ,  $-C(O)NR^2-$ ,  $-NR^2C(O)-$ ,  $-NR^2C(O)NR^2-$ ,  $-NR^2-$ ,  
25 and O;

Y is  $NR^2R^{2a}$ , provided that X-Y do not form a N-N or O-N bond;  
alternatively, Y is selected from one of the following  
30 carbocyclic and heterocyclic systems which are substituted with 0-2  $R^{4a}$ ;

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl,

1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl,  
1,2,4-triazolyl, 1,2,5-triazolyl, and 1,3,4-triazolyl;

5        R<sup>4</sup>, at each occurrence, is selected from =O, OH, Cl, F, C<sub>1-4</sub>  
alkyl, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, (CH<sub>2</sub>)<sub>r</sub>C(O)R<sup>2b</sup>, NR<sup>2</sup>C(O)R<sup>2b</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>,  
CH(=NH)NH<sub>2</sub>, NHC(=NH)NH<sub>2</sub>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>SO<sub>2</sub>-C<sub>1-4</sub> alkyl,  
NR<sup>2</sup>SO<sub>2</sub>R<sup>5</sup>, S(O)<sub>p</sub>R<sup>5</sup>, and (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>;

10      R<sup>4a</sup>, at each occurrence, is selected from =O, OH, Cl, F, C<sub>1-4</sub>  
alkyl, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, (CH<sub>2</sub>)<sub>r</sub>C(O)R<sup>2b</sup>, NR<sup>2</sup>C(O)R<sup>2b</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>,  
CH(=NH)NH<sub>2</sub>, NHC(=NH)NH<sub>2</sub>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>SO<sub>2</sub>-C<sub>1-4</sub> alkyl,  
NR<sup>2</sup>SO<sub>2</sub>R<sup>5</sup>, S(O)<sub>p</sub>R<sup>5</sup>, (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>, and 1-CF<sub>3</sub>-tetrazol-2-yl;

15      R<sup>5</sup>, at each occurrence, is selected from CF<sub>3</sub>, C<sub>1-6</sub> alkyl,  
phenyl substituted with 0-2 R<sup>6</sup>, and benzyl substituted  
with 0-2 R<sup>6</sup>;

20      R<sup>6</sup>, at each occurrence, is selected from H, =O, OH, OR<sup>2</sup>, Cl,  
F, CH<sub>3</sub>, CN, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, (CH<sub>2</sub>)<sub>r</sub>C(O)R<sup>2b</sup>, NR<sup>2</sup>C(O)R<sup>2b</sup>,  
CH(=NH)NH<sub>2</sub>, NHC(=NH)NH<sub>2</sub>, and SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>;

25      R<sup>7</sup>, at each occurrence, is selected from H, OH, C<sub>1-6</sub> alkyl,  
C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy, C<sub>1-4</sub> alkoxycarbonyl,  
benzyl, C<sub>6-10</sub> aryloxy, C<sub>6-10</sub> aryloxycarbonyl, C<sub>6-10</sub>  
arylmethylcarbonyl, C<sub>1-4</sub> alkylcarbonyloxy C<sub>1-4</sub>  
alkoxycarbonyl, C<sub>6-10</sub> arylcarbonyloxy C<sub>1-4</sub> alkoxycarbonyl,  
C<sub>1-6</sub> alkylaminocarbonyl, phenylaminocarbonyl, and phenyl  
C<sub>1-4</sub> alkoxycarbonyl;

30      R<sup>8</sup>, at each occurrence, is selected from H, C<sub>1-6</sub> alkyl and  
benzyl; and

alternatively, R<sup>7</sup> and R<sup>8</sup> combine to form a morpholino group;  
and,

35      R<sup>9</sup>, at each occurrence, is selected from H, C<sub>1-6</sub> alkyl and  
benzyl.

[13] In another further preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib, wherein;

5 E is phenyl substituted with R or 2-pyridyl substituted with R;

R is selected from H, Cl, F, OCH<sub>3</sub>, CH<sub>3</sub>, OCF<sub>3</sub>, and CF<sub>3</sub>;

10 Z is selected from a C(O)CH<sub>2</sub> and C(O)NH, provided that Z does not form a N-N bond with group A;

R<sup>1a</sup>, at each occurrence, is selected from H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, Cl, F, CF<sub>3</sub>, OCH<sub>3</sub>, NR<sup>2</sup>R<sup>2a</sup>, S(O)<sub>p</sub>R<sup>2b</sup>, CH<sub>2</sub>S(O)<sub>p</sub>R<sup>2b</sup>,

15 CH<sub>2</sub>NR<sup>2</sup>S(O)<sub>p</sub>R<sup>2b</sup>, C(O)R<sup>2c</sup>, CH<sub>2</sub>C(O)R<sup>2c</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>, and SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>;

R<sup>1b</sup> is selected from H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, Cl, F, CF<sub>3</sub>, OCH<sub>3</sub>, NR<sup>2</sup>R<sup>2a</sup>, S(O)<sub>p</sub>R<sup>2b</sup>, CH<sub>2</sub>S(O)<sub>p</sub>R<sup>2b</sup>, CH<sub>2</sub>NR<sup>2</sup>S(O)<sub>p</sub>R<sup>2b</sup>, C(O)R<sup>2c</sup>, CH<sub>2</sub>C(O)R<sup>2c</sup>,

20 C(O)NR<sup>2</sup>R<sup>2a</sup>, and SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>;

R<sup>1c</sup> is selected from H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CF<sub>3</sub>, CH<sub>2</sub>S(O)<sub>p</sub>R<sup>2b</sup>, CH<sub>2</sub>NR<sup>2</sup>S(O)<sub>p</sub>R<sup>2b</sup>, C(O)R<sup>2c</sup>, CH<sub>2</sub>C(O)R<sup>2c</sup>, and C(O)NR<sup>2</sup>R<sup>2a</sup>;

25 A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R<sup>4</sup>; phenyl, pyridyl, pyrimidyl, furanyl, thiophenyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, and imidazolyl;

30

B is selected from: Y and X-Y;

X is selected from CH<sub>2</sub>, -CR<sup>2</sup>(CR<sup>2</sup>R<sup>2b</sup>)-, -C(O)-, -C(=NR)-, -CH(NR<sup>2</sup>R<sup>2a</sup>)-, -C(O)NR<sup>2</sup>-, -NR<sup>2</sup>C(O)-, -NR<sup>2</sup>C(O)NR<sup>2</sup>-, -NR<sup>2</sup>-,

35 and O;

Y is NR<sup>2</sup>R<sup>2a</sup>, provided that X-Y do not form a N-N or O-N bond;

alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R<sup>4a</sup>;

5 phenyl, piperidinyl, piperazinyl, pyridyl,  
pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl,  
pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl,  
thiazolyl, isothiazolyl, pyrazolyl, imidazolyl,  
oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,  
10 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,  
1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl,  
1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl,  
15 1,2,4-triazolyl, 1,2,5-triazolyl, and 1,3,4-triazolyl;

R<sup>2</sup>, at each occurrence, is selected from H, CF<sub>3</sub>, CH<sub>3</sub>, benzyl,  
15 and phenyl;

R<sup>2a</sup>, at each occurrence, is selected from H, CF<sub>3</sub>, CH<sub>3</sub>, benzyl,  
and phenyl;

20 R<sup>2b</sup>, at each occurrence, is selected from CF<sub>3</sub>, OCH<sub>3</sub>, CH<sub>3</sub>,  
benzyl, and phenyl;

R<sup>2c</sup>, at each occurrence, is selected from CF<sub>3</sub>, OH, OCH<sub>3</sub>, CH<sub>3</sub>,  
benzyl, and phenyl;

25 alternatively, R<sup>2</sup> and R<sup>2a</sup> combine to form a 5 or 6 membered  
saturated, partially unsaturated, or unsaturated ring  
which contains from 0-1 additional heteroatoms selected  
from the group consisting of N, O, and S;

30 R<sup>3</sup>, at each occurrence, is selected from H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, and  
phenyl;

35 R<sup>3a</sup>, at each occurrence, is selected from H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, and  
phenyl;

$R^4$ , at each occurrence, is selected from OH, Cl, F,  $CH_3$ ,  $CH_2CH_3$ ,  $NR^2R^{2a}$ ,  $CH_2NR^2R^{2a}$ ,  $C(O)R^{2b}$ ,  $NR^2C(O)R^{2b}$ ,  $C(O)NR^2R^{2a}$ , and  $CF_3$ ;

5    $R^{4a}$ , at each occurrence, is selected from OH, Cl, F,  $CH_3$ ,  $CH_2CH_3$ ,  $NR^2R^{2a}$ ,  $CH_2NR^2R^{2a}$ ,  $C(O)R^{2b}$ ,  $C(O)NR^2R^{2a}$ ,  $SO_2NR^2R^{2a}$ ,  $S(O)_pR^5$ ,  $CF_3$ , and 1- $CF_3$ -tetrazol-2-yl;

10    $R^5$ , at each occurrence, is selected from  $CF_3$ ,  $C_{1-6}$  alkyl, phenyl substituted with 0-2  $R^6$ , and benzyl substituted with 1  $R^6$ ;

15    $R^6$ , at each occurrence, is selected from H, OH,  $OCH_3$ , Cl, F,  $CH_3$ , CN,  $NO_2$ ,  $NR^2R^{2a}$ ,  $CH_2NR^2R^{2a}$ , and  $SO_2NR^2R^{2a}$ ;

20    $R^7$ , at each occurrence, is selected from H, OH,  $C_{1-3}$  alkyl,  $C_{1-3}$  alkylcarbonyl,  $C_{1-3}$  alkoxy,  $C_{1-4}$  alkoxycarbonyl, benzyl, phenoxy, phenoxy carbonyl, benzyl carbonyl,  $C_{1-4}$  alkylcarbonyloxy,  $C_{1-4}$  alkoxy carbonyl, phenyl carbonyloxy,  $C_{1-4}$  alkoxy carbonyl,  $C_{1-6}$  alkylaminocarbonyl, phenylaminocarbonyl, and phenyl  $C_{1-4}$  alkoxy carbonyl;

25    $R^8$ , at each occurrence, is selected from H,  $CH_3$ , and benzyl; and,

30   alternatively,  $R^7$  and  $R^8$  combine to form a morpholino group;

35    $R^9$ , at each occurrence, is selected from H,  $CH_3$ , and benzyl.

[14] In another still further preferred embodiment, the present invention provides novel compounds of formulae Ia-Ib, wherein;

35    $R^{1a}$ , at each occurrence, is selected from H,  $CH_3$ ,  $CH_2CH_3$ , Cl, F,  $CF_3$ ,  $OCH_3$ ,  $NR^2R^{2a}$ ,  $S(O)_pR^{2b}$ ,  $C(O)NR^2R^{2a}$ ,  $CH_2S(O)_pR^{2b}$ ,  $CH_2NR^2S(O)_pR^{2b}$ ,  $C(O)R^{2c}$ ,  $CH_2C(O)R^{2c}$ , and  $SO_2NR^2R^{2a}$ ;

R<sup>1b</sup> is selected from H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, Cl, F, CF<sub>3</sub>, OCH<sub>3</sub>, NR<sup>2a</sup>R<sup>2a</sup>, S(O)<sub>p</sub>R<sup>2b</sup>, C(O)NR<sup>2a</sup>R<sup>2a</sup>, CH<sub>2</sub>S(O)<sub>p</sub>R<sup>2b</sup>, CH<sub>2</sub>NR<sup>2a</sup>S(O)<sub>p</sub>R<sup>2b</sup>, C(O)R<sup>2b</sup>, CH<sub>2</sub>C(O)R<sup>2b</sup>, and SO<sub>2</sub>NR<sup>2a</sup>R<sup>2a</sup>;

5 R<sup>1c</sup> is selected from H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CF<sub>3</sub>, C(O)NR<sup>2a</sup>R<sup>2a</sup>, CH<sub>2</sub>S(O)<sub>p</sub>R<sup>2b</sup>, CH<sub>2</sub>NR<sup>2a</sup>S(O)<sub>p</sub>R<sup>2b</sup>, C(O)R<sup>2b</sup>, and CH<sub>2</sub>C(O)R<sup>2b</sup>;

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R<sup>4</sup>;  
10 phenyl, pyridyl, and pyrimidyl;

B is selected from: Y and X-Y;  
/

X is selected from -C(O)- and O;

15 Y is NR<sup>2a</sup>R<sup>2a</sup>, provided that X-Y do not form a O-N bond;

alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R<sup>4a</sup>;  
20 phenyl, piperazinyl, pyridyl, pyrimidyl, morpholinyl, pyrrolidinyl, imidazolyl, and 1,2,3-triazolyl;

25 R<sup>2</sup>, at each occurrence, is selected from H, CF<sub>3</sub>, CH<sub>3</sub>, benzyl, and phenyl;

R<sup>2a</sup>, at each occurrence, is selected from H, CF<sub>3</sub>, CH<sub>3</sub>, benzyl, and phenyl;

30 R<sup>2b</sup>, at each occurrence, is selected from CF<sub>3</sub>, OCH<sub>3</sub>, CH<sub>3</sub>, benzyl, and phenyl;

R<sup>2c</sup>, at each occurrence, is selected from CF<sub>3</sub>, OH, OCH<sub>3</sub>, CH<sub>3</sub>, benzyl, and phenyl;

alternatively, R<sup>2</sup> and R<sup>2a</sup> combine to form a ring system selected from pyrrolidinyl, piperazinyl and morpholino;

R<sup>4</sup>, at each occurrence, is selected from Cl, F, CH<sub>3</sub>, NR<sup>2</sup>R<sup>2a</sup>, and CF<sub>3</sub>;

5 R<sup>4a</sup>, at each occurrence, is selected from Cl, F, CH<sub>3</sub>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, S(O)<sub>p</sub>R<sup>5</sup>, and CF<sub>3</sub>; and,

R<sup>5</sup>, at each occurrence, is selected from CF<sub>3</sub> and CH<sub>3</sub>.

10

[15] Specifically preferred compounds of the present invention are selected from the group:

15 1-(3-amidinophenyl)-5-[(2'-methylsulfonyl-[1,1']-biphen-4-yl)-aminocarbonyl]-3-trifluoromethyl-pyrazoline; and,

1-(3-aminomethylphenyl)-5-[(2'-methylsulfonyl-[1,1']-biphen-4-yl)-aminocarbonyl]-3-trifluoromethyl-pyrazoline;

20 and pharmaceutically acceptable salts thereof.

In a second embodiment, the present invention provides novel pharmaceutical compositions, comprising: a  
25 pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

In a third embodiment, the present invention provides a  
30 novel method for treating or preventing a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

35

#### DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an

asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

When any variable (e.g., R<sup>6</sup>) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R<sup>6</sup>, then said group may optionally be substituted with up to two R<sup>6</sup> groups and R<sup>6</sup> at each occurrence is selected independently from the definition of R<sup>6</sup>. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "C<sub>1-6</sub> alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, examples of which include, but are not limited to, methyl, ethyl,  
5 n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, and hexyl; "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as  
10 ethenyl, propenyl, and the like.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, and the like.

15 As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7- to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to,  
20 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

25 As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5- to 7- membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and  
30 from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached  
35 to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically

noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred  
5 that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5- to 7-membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and  
10 from 1 to 4 heterotams independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to,  
15 1H-indazole, 2-pyrrolidonyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidonyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl,  
20 benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl,  $\beta$ -carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl., oxazolyl, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxythiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidonyl, 4-piperidonyl, pteridinyl, purinyl,  
30 pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridoaxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl,

quinoxalinyl, quinuclidinyl, carbolinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl,  
5 thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl. Preferred heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, indolyl,  
10 benzimidazolyl, 1*H*-indazolyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The phrase "pharmaceutically acceptable" is employed  
15 herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or  
20 complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof.  
25 Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or  
30 organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic,

sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are intended to include any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula (I) are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of formula (I) wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug or compound of formula (I) is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formula (I), and the like. Preferred prodrugs are amidine prodrugs wherein D is C(=NR<sup>7</sup>)NH<sub>2</sub> or its tautomer C(=NH)NHR<sup>7</sup> and R<sup>7</sup> is selected from OH, C<sub>1-4</sub> alkoxy, C<sub>6-10</sub> aryloxy, C<sub>1-4</sub> alkoxycarbonyl, C<sub>6-10</sub> aryloxycarbonyl, C<sub>6-10</sub> arylmethylcarbonyl, C<sub>1-4</sub> alkylcarbonyloxy C<sub>1-4</sub> alkoxycarbonyl, and C<sub>6-10</sub> arylcarbonyloxy C<sub>1-4</sub> alkoxycarbonyl. More preferred prodrugs are where R<sup>7</sup> is

OH, methoxy, ethoxy, benzyloxycarbonyl, methoxycarbonyl, and methylcarbonyloxymethoxycarbonyl.

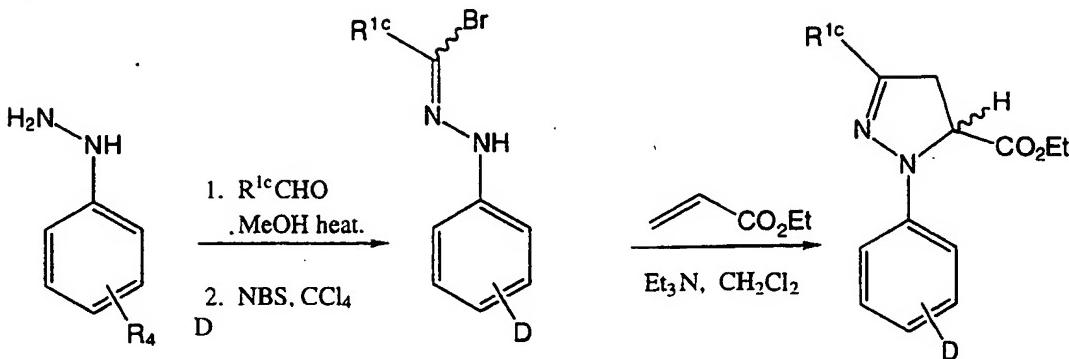
"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive 5 isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

#### SYNTHESIS

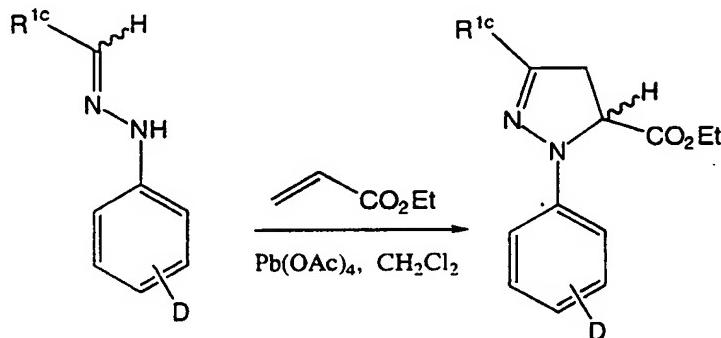
10 The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being 15 effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular 20 process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups 25 present in the compounds described in this invention. An authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Wiley and Sons, 1991). All references cited herein are hereby incorporated in their entirety herein 30 by reference.

35 Pyrazolines of this invention can be easily prepared via [3+2] cycloaddition of bromo or chloro hydrazone with an appropriate acrylate according to the methodology described by

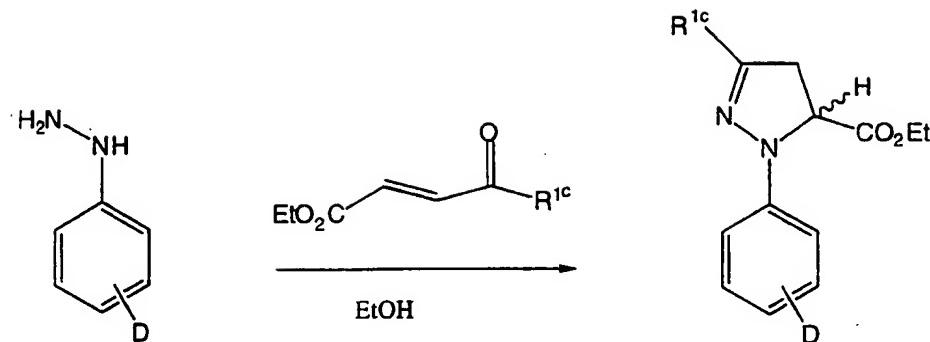
Tewari R. S. and Parihar *Tetrahedron* **1983**, *39*, 129-136, or  
 Krayushkin, M. M. et. al *Izv. Akad. Nauk, Ser. Khim.* **1994**, *1*,  
 114-117.



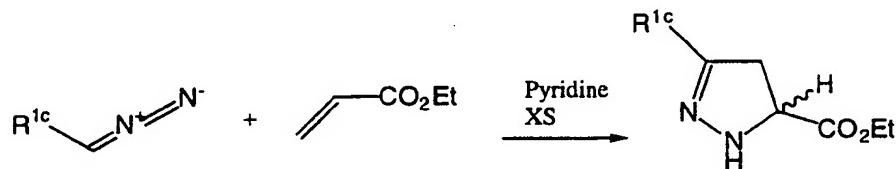
Pyrazoline 5-esters can also be prepared by the treatment of an appropriately substituted hydrazone with lead tetraacetate and an appropriate acrylate in a THF/benzene solvent system according to the procedure of Sasaki T, et. al. *Bull. Chem Soc. Jpn.* **1970**, *43*, 1254.



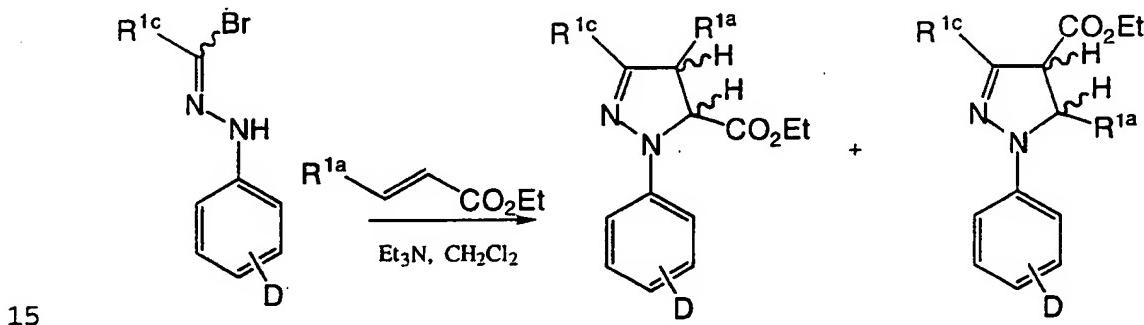
15 Another method of obtaining pyrazoline 5-esters is the condensation of an appropriate phenyl or heteroaryl hydrazine with an appropriate 2-oxoglutaconate according to Blitzke, T. et. al. *J. Prakt. Chem.* **1993**, *335*(8), 683.



Alternatively the pyrazoline ester can be prepared by treatment of a diazo-trifluoromethyl derivative with excess 5 acrylate or acrolein in the presence of excess pyridine (Doyle, M. O. et. al. *J. Heterocyclic Chem.* 1983, 20, 943).



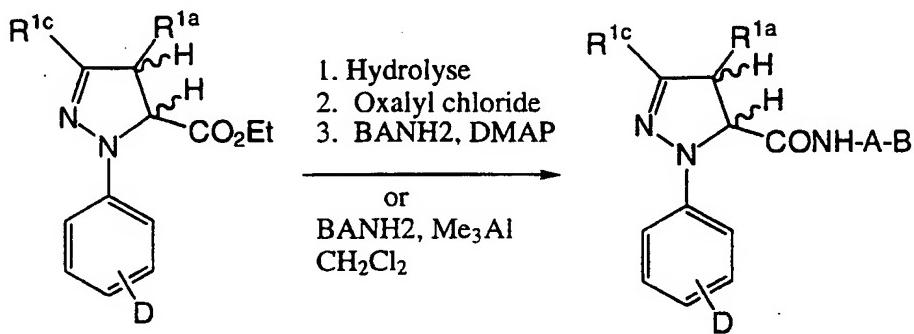
10 Cycloadditions as described above but with di-substituted olefins should result in the formation of regio-adducts which can be easily separated by standard chromatographic techniques.



It is understood by those in the art of organic synthesis that such cycloadditions can also be carried out with a wide variety of electron withdrawing olefins with functionalities 20 such as nitro, sulfonyl, sulfonamido, nitrile, phosphate etc. These in turn can be derivatized to appropriate compounds of the present invention.

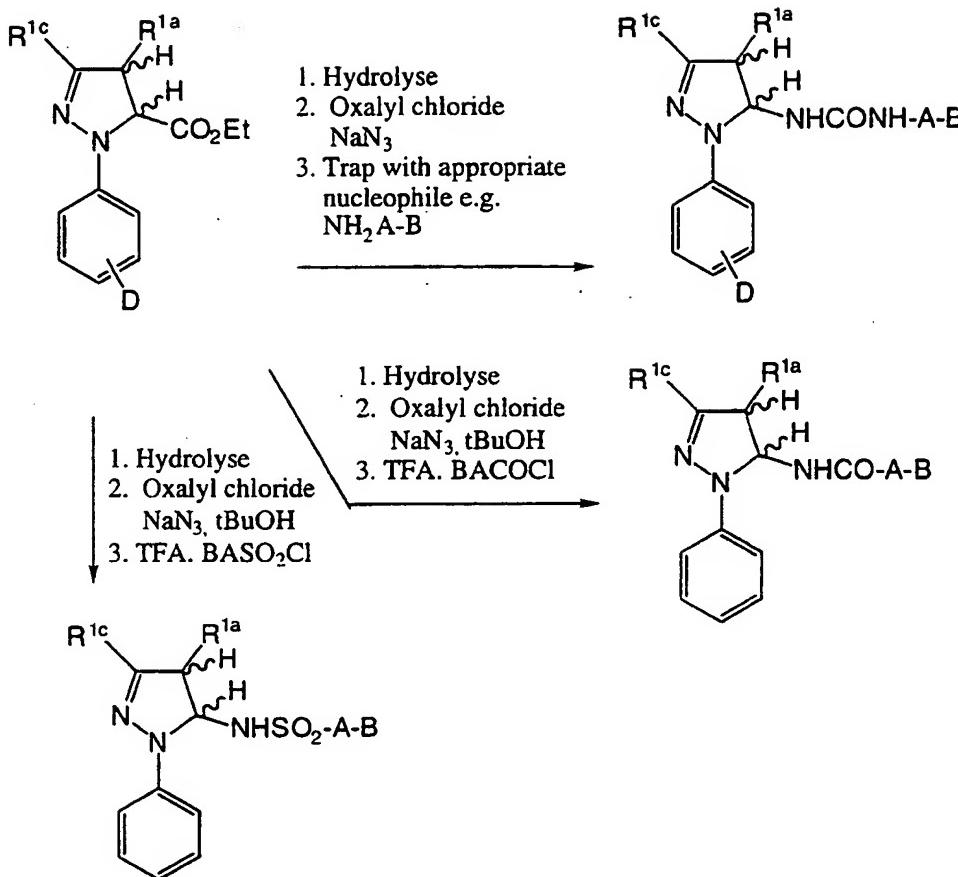
The pyrazoline carboxyesters obtained via any of the above mentioned methodologies can be converted to the amide derivatives via the acid, acid chloride coupling methodologies or a direct Weinreb (trimethylaluminum, aniline in dichloromethane) coupling technique known to those in the art of organic synthesis. A variety of anilines or amines can be coupled via these methodologies to afford the desired compounds.

10



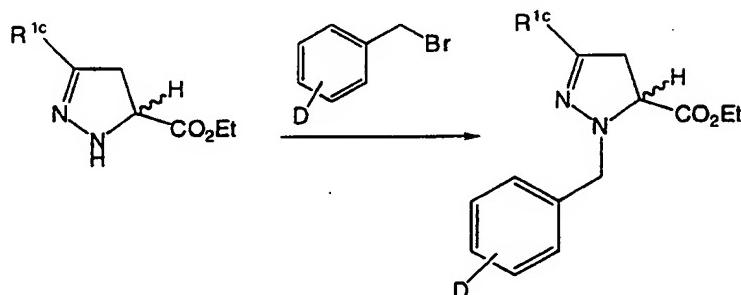
15

Alternatively the ester can be hydrolysed and converted to an amino functionality via the Curtius rearrangement. This in turn can be derivatised to obtain an amido, sulfonamido or urea derivative.



Pyrazolines wherein s is other than 0 can be prepared by alkylation of an appropriate pyrazoline.

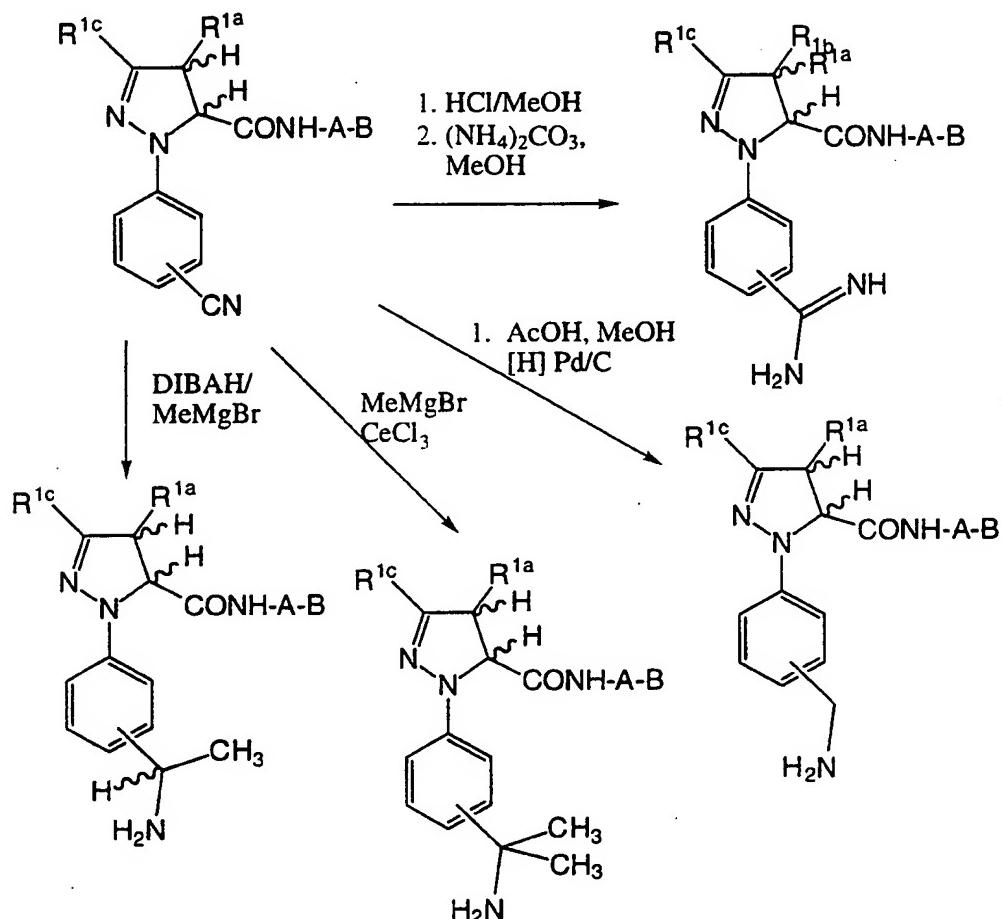
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The electrophile can consist of simple alkyl halides to heteroaryl alkyl halides. Some of the heteroaryl alkyl groups 10 can include pyridyl, pyrimidyl, imidazolyl etc.

In cases wherein D is a nitrile can be further converted to an amidine functionality via the standard Pinner-amidine reaction sequence known to those in the art or can be

converted to the benzylamine via reduction in an acidic media or can be converted to the secondary and tertiary amine via the DIBAH/MeMgCl or MeMgBr/CeCl<sub>3</sub> methodologies outlined below.

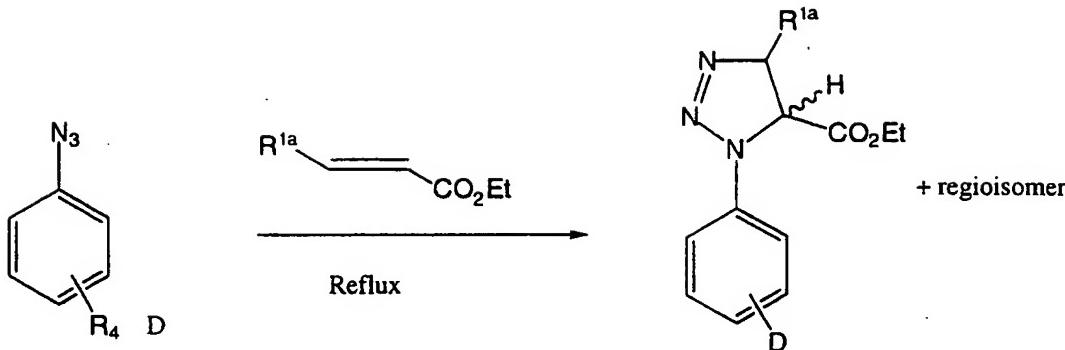


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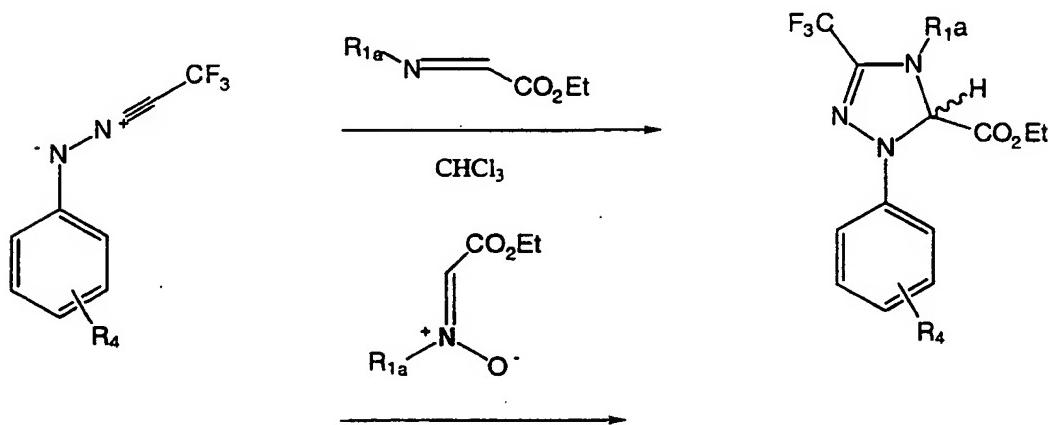
Compounds wherein D is a nitro can be reduced under catalytic Pd/C/MeOH techniques or SnCl<sub>2</sub>/EtOAc or Zn/AcOH conditions to afford the desired amino derivatives.

Enantiomers of the pyrazolines can be easily obtained either via lipase hydrolysis of its esters or resolution with common chiral bases known to those in the art.

1,2,3-Triazolines can be synthesized via the cycloaddition methodology however in this case the dipole is an aryl azide and the dipolarophile is a variety of olefins bearing an electron withdrawing group such as an ester, amide or sulfonamide.



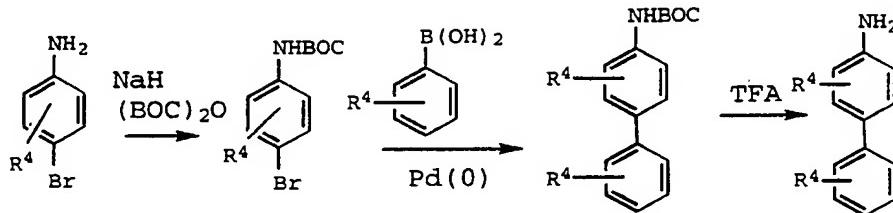
1,2,4-Triazolines can be prepared via the methods of Sandhy J. S. et. al. *Heterocycles* 1985, 23(5), 1143, and 5 *Heterocycles* 1985, 23(5), 1123, by the method described in the scheme below.



10 The triazoline esters can then subjected to the standard coupling procedures discussed above to afford the desired amide analogs. These can then further modified to the prepare compounds of the present invention.

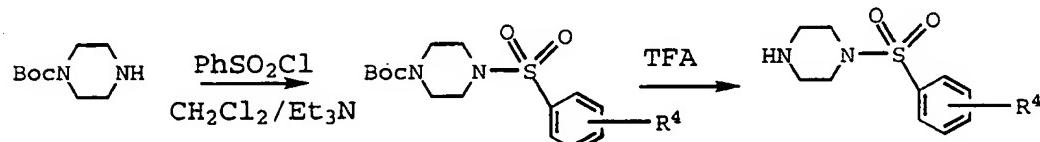
Compounds of the present invention wherein AB is a biphenylamine or similar amine may be prepared as shown in the following scheme. 4-Bromoaniline can be protected as Boc-15 derivative and coupled to a phenylboronic acid under Suzuki conditions (*Bioorg. Med. Chem. Lett.* 1994, 189). Deprotection with TFA provides the aminobiphenyl compound. Other similar amines wherein A and/or B are heterocycles can be prepared by the same method using appropriately substituted 20 boronic acids and arylbromide. The bromoaniline can also be

linked to the core ring structures first as described above, and then undergo a Suzuki reaction to give the desired product.



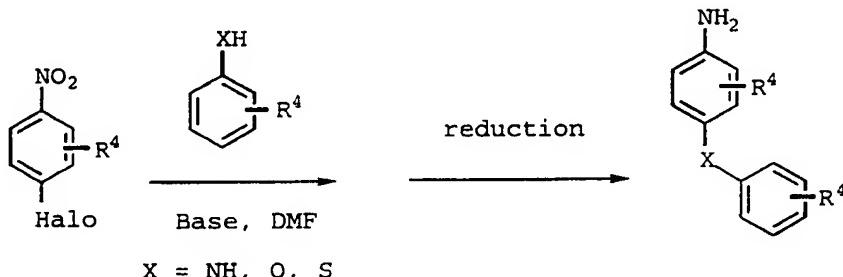
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Compounds of the present invention wherein A-B is A-X-Y can be prepared like the piperazine derivative shown below.



10

The following scheme shows how one can couple cyclic groups wherein X=NH, O, or S.



15

When B is defined as X-Y, the following description applies. Groups A and B are available either through commercial sources, known in the literature or readily synthesized by the adaptation of standard procedures known to practitioners skilled in the art of organic synthesis. The required reactive functional groups appended to analogs of A and B are also available either through commercial sources, known in the literature or readily synthesized by the adaptation of standard procedures known to practitioners skilled in the art of organic synthesis. In the tables that follow

the chemistry required to effect the coupling of A to B is outlined.

5      **Table A: Preparation of Amide, Ester, Urea, Sulfonamide and Sulfamide linkages between A and B.**

Rxn. No.	if A contains :	then the reactive substituent of Y is :	to give the following product A-X-Y :
1	A-NHR <sup>2</sup> as a substituent	ClC(O)-Y	A-NR <sup>2</sup> -C(O)-Y
2	a secondary NH as part of a ring or chain	ClC(O)-Y	A-C(O)-Y
3	A-OH as a substituent	ClC(O)-Y	A-O-C(O)-Y
4	A-NHR <sup>2</sup> as a substituent	ClC(O)-CR <sup>2</sup> R <sup>2a</sup> -Y	A-NR <sup>2</sup> -C(O)-CR <sup>2</sup> R <sup>2a</sup> -Y
5	a secondary NH as part of a ring or chain	ClC(O)-CR <sup>2</sup> R <sup>2a</sup> -Y	A-C(O)-CR <sup>2</sup> R <sup>2a</sup> -Y
6	A-OH as a substituent	ClC(O)-CR <sup>2</sup> R <sup>2a</sup> -Y	A-O-C(O)-CR <sup>2</sup> R <sup>2a</sup> -Y
7	A-NHR <sup>3</sup> as a substituent	ClC(O)NR <sup>2</sup> -Y	A-NR <sup>2</sup> -C(O)NR <sup>2</sup> -Y
8	a secondary NH as part of a ring or chain	ClC(O)NR <sup>2</sup> -Y	A-C(O)NR <sup>2</sup> -Y
9	A-OH as a substituent	ClC(O)NR <sup>2</sup> -Y	A-O-C(O)NR <sup>2</sup> -Y
10	A-NHR <sup>2</sup> as a substituent	ClSO <sub>2</sub> -Y	A-NR <sup>2</sup> -SO <sub>2</sub> -Y
11	a secondary NH as part of a ring or chain	ClSO <sub>2</sub> -Y	A-SO <sub>2</sub> -Y
12	A-NHR <sup>2</sup> as a substituent	ClSO <sub>2</sub> -CR <sup>2</sup> R <sup>2a</sup> -Y	A-NR <sup>2</sup> -SO <sub>2</sub> -CR <sup>2</sup> R <sup>2a</sup> -Y

13	a secondary NH as part of a ring or chain	$\text{ClSO}_2-\text{CR}^2\text{R}^{2a}-\text{Y}$	$\text{A-SO}_2-\text{CR}^2\text{R}^{2a}-\text{Y}$
14	$\text{A-NHR}^2$ as a substituent	$\text{ClSO}_2-\text{NR}^2-\text{Y}$	$\text{A-NR}^2-\text{SO}_2-\text{NR}^2-\text{Y}$
15	a secondary NH as part of a ring or chain	$\text{ClSO}_2-\text{NR}^2-\text{Y}$	$\text{A-SO}_2-\text{NR}^2-\text{Y}$
16	$\text{A-C(O)Cl}$	HO-Y as a substituent	$\text{A-C(O)-O-Y}$
17	$\text{A-C(O)Cl}$	$\text{NHR}^2-\text{Y}$ as a substituent	$\text{A-C(O)-NR}^2-\text{Y}$
18	$\text{A-C(O)Cl}$	a secondary NH as part of a ring or chain	$\text{A-C(O)-Y}$
19	$\text{A-CR}^2\text{R}^{2a}\text{C(O)Cl}$	HO-Y as a substituent	$\text{A-CR}^2\text{R}^{2a}\text{C(O)-O-Y}$
20	$\text{A-CR}^2\text{R}^{2a}\text{C(O)Cl}$	$\text{NHR}^2-\text{Y}$ as a substituent	$\text{A-CR}^2\text{R}^{2a}\text{C(O)-NR}^2-\text{Y}$
21	$\text{A-CR}^2\text{R}^{2a}\text{C(O)Cl}$	a secondary NH as part of a ring or chain	$\text{A-CR}^2\text{R}^{2a}\text{C(O)-Y}$
22	$\text{A-SO}_2\text{Cl}$	$\text{NHR}^2-\text{Y}$ as a substituent	$\text{A-SO}_2-\text{NR}^2-\text{Y}$
23	$\text{A-SO}_2\text{Cl}$	a secondary NH as part of a ring or chain	$\text{A-SO}_2-\text{Y}$
24	$\text{A-CR}^2\text{R}^{2a}\text{SO}_2\text{Cl}$	$\text{NHR}^2-\text{Y}$ as a substituent	$\text{A-CR}^2\text{R}^{2a}\text{SO}_2-\text{NR}^2-\text{Y}$
25	$\text{A-CR}^2\text{R}^{2a}\text{SO}_2\text{Cl}$	a secondary NH as part of a ring or chain	$\text{A-CR}^2\text{R}^{2a}\text{SO}_2-\text{Y}$

The chemistry of Table A can be carried out in aprotic solvents such as a chlorocarbon, pyridine, benzene or toluene, at temperatures ranging from -20 °C to the reflux point of the solvent and with or without a trialkylamine base.

**Table B: Preparation of ketone linkages between A and B.**

Rxn. No.	if A contains :	then the reactive substituent of Y is :	to give the following product A-X-Y :
1	A-C(O)Cl	BrMg-Y	A-C(O)-Y
2	A-CR <sup>2</sup> R <sup>2a</sup> C(O)Cl	BrMg-Y	A-CR <sup>2</sup> R <sup>2a</sup> C <sub>2</sub> C(O)-Y
3	A-C(O)Cl	BrMgCR <sup>2</sup> R <sup>2a</sup> -Y	A-C(O)CR <sup>2</sup> R <sup>2a</sup> -Y
4	A-CR <sup>2</sup> R <sup>2a</sup> C(O)Cl	BrMgCR <sup>2</sup> R <sup>2a</sup> -Y	A-CR <sup>2</sup> R <sup>2a</sup> C(O)CR <sup>2</sup> R <sup>2a</sup> -Y

5       The coupling chemistry of Table B can be carried out by a variety of methods. The Grignard reagent required for Y is prepared from a halogen analog of Y in dry ether, dimethoxyethane or tetrahydrofuran at 0°C to the reflux point of the solvent. This Grignard reagent can be reacted directly under very controlled conditions, that is low temeprature (-20°C or lower) and with a large excess of acid chloride or with catalytic or stoichiometric copper bromide-dimethyl sulfide complex in dimethyl sulfide as a solvent or with a variant thereof. Other methods available include transforming 10 the Grignard reagent to the cadmium reagent and coupling according to the procedure of Carson and Prout (Org. Syn. Col. Vol. 3 (1955) 601) or a coupling mediated by Fe(acac)<sub>3</sub> according to Fiandanese et al. (Tetrahedron Lett., (1984) 4805), or a coupling mediated by manganese (II) catalysis 15 (Cahiez and Laboue, Tetrahedron Lett., 33(31), (1992) 4437). 20

**Table C: Preparation of ether and thioether linkages between A and B**

Rxn. No.	if A contains :	then the reactive substituent of Y is :	to give the following product A-X-Y :
1	A-OH	Br-Y	A-O-Y
2	A-CR <sup>2</sup> R <sup>2a</sup> -OH	Br-Y	A-CR <sup>2</sup> R <sup>2a</sup> O-Y
3	A-OH	Br-CR <sup>2</sup> R <sup>2a</sup> -Y	A-OCR <sup>2</sup> R <sup>2a</sup> -Y
4	A-SH	Br-Y	A-S-Y
5	A-CR <sup>2</sup> R <sup>2a</sup> -SH	Br-Y	A-CR <sup>2</sup> R <sup>2a</sup> S-Y
6	A-SH	Br-CR <sup>2</sup> R <sup>2a</sup> -Y	A-SCR <sup>2</sup> R <sup>2a</sup> -Y

The ether and thioether linkages of Table C can be prepared by reacting the two components in a polar aprotic solvent such as acetone, dimethylformamide or dimethylsulfoxide in the presence of a base such as potassium carbonate, sodium hydride or potassium t-butoxide at temperature ranging from ambient temperature to the reflux point of the solvent used.

**Table D: Preparation of -SO- and -SO<sub>2</sub>- linkages from thioethers of Table 3.**

Rxn. No.	if the starting material is :	and it is oxidized with Alumina (wet)/ Oxone (Greenhalgh, Synlett, (1992) 235) the product is :	and it is oxidized with m-chloroper- benzoic acid (Satoh et al., Chem. Lett. (1992) 381), the product is :
1	A-S-Y	A-S(O)-Y	A-SO <sub>2</sub> -Y
2	A-CR <sup>2</sup> R <sup>2a</sup> S-Y	A-CR <sup>2</sup> R <sup>2a</sup> S(O)-Y	A-CR <sup>2</sup> R <sup>2a</sup> SO <sub>2</sub> -Y
3	A-SCR <sup>2</sup> R <sup>2a</sup> -Y	A-S(O)CR <sup>2</sup> R <sup>2a</sup> -Y	A-SO <sub>2</sub> CR <sup>2</sup> R <sup>2a</sup> -Y

The thioethers of Table C serve as a convenient starting material for the preparation of the sulfoxide and sulfone analogs of Table D. A combination of wet alumina and oxone can provide a reliable reagent for the oxidation of the

thioether to the sulfoxide while m-chloroperbenzoic acid oxidation will give the sulfone.

**Table E: Methods of Preparing Group E**

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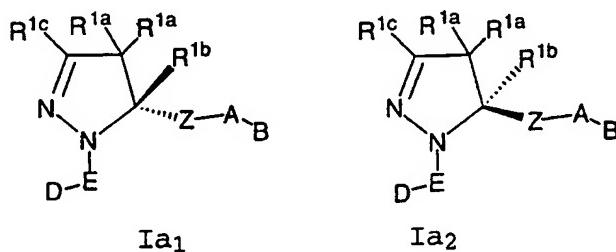
Rxn	Q	D is to be	then a transformation that may be used is :
1	-CN	-C(=NH)NH <sub>2</sub>	$\begin{array}{c} \text{E}-\text{C}\equiv\text{N} \\ \xrightarrow{\substack{\text{i) HCl MeOH} \\ \text{ii) NH}_3\text{OAc, MeOH}}} \end{array} \begin{array}{c} \text{NH}_2 \\ \diagdown \\ \text{E}-\text{C}=\text{N} \\ \diagup \\ \text{NH} \end{array}$
2	-CN	-CH <sub>2</sub> NH <sub>2</sub>	$\begin{array}{c} \text{E}-\text{C}\equiv\text{N} \\ \xrightarrow{\substack{\text{LiAlH}_4 \\ \text{Et}_2\text{O}}} \end{array} \text{E}-\text{CH}_2\text{NH}_2$
3	-CO <sub>2</sub> H	-CH <sub>2</sub> NH <sub>2</sub>	$\begin{array}{c} \text{E}-\text{C}(=\text{O})\text{OH} \\ \xrightarrow{\substack{\text{i) iBuOC(O)Cl} \\ \text{NMM, THF} \\ \text{then NaBH}_4, \text{H}_2\text{O/THF}}} \end{array} \text{E}-\text{CH}_2\text{NH}_2$ $\begin{array}{c} \text{E}-\text{C}(=\text{O})\text{OH} \\ \xrightarrow{\substack{\text{ii) MsCl, Et}_3\text{N, CH}_2\text{Cl}_2} \\ \text{iii) NaN}_3, \text{DMF} \\ \text{iv) SnCl}_2, \text{MeOH}}} \end{array}$
4	-CO <sub>2</sub> H	-NH <sub>2</sub>	$\begin{array}{c} \text{E}-\text{C}(=\text{O})\text{OH} \\ \xrightarrow{\substack{\text{i) iBuOC(O)Cl} \\ \text{NMM, THF} \\ \text{then NaN}_3 \text{ and heat}}} \end{array} \text{E}-\text{NH}_2$ $\begin{array}{c} \text{E}-\text{C}(=\text{O})\text{OH} \\ \xrightarrow{\substack{\text{ii) tBuOH, reflux} \\ \text{iii) HCl, Et}_2\text{O}}} \end{array}$

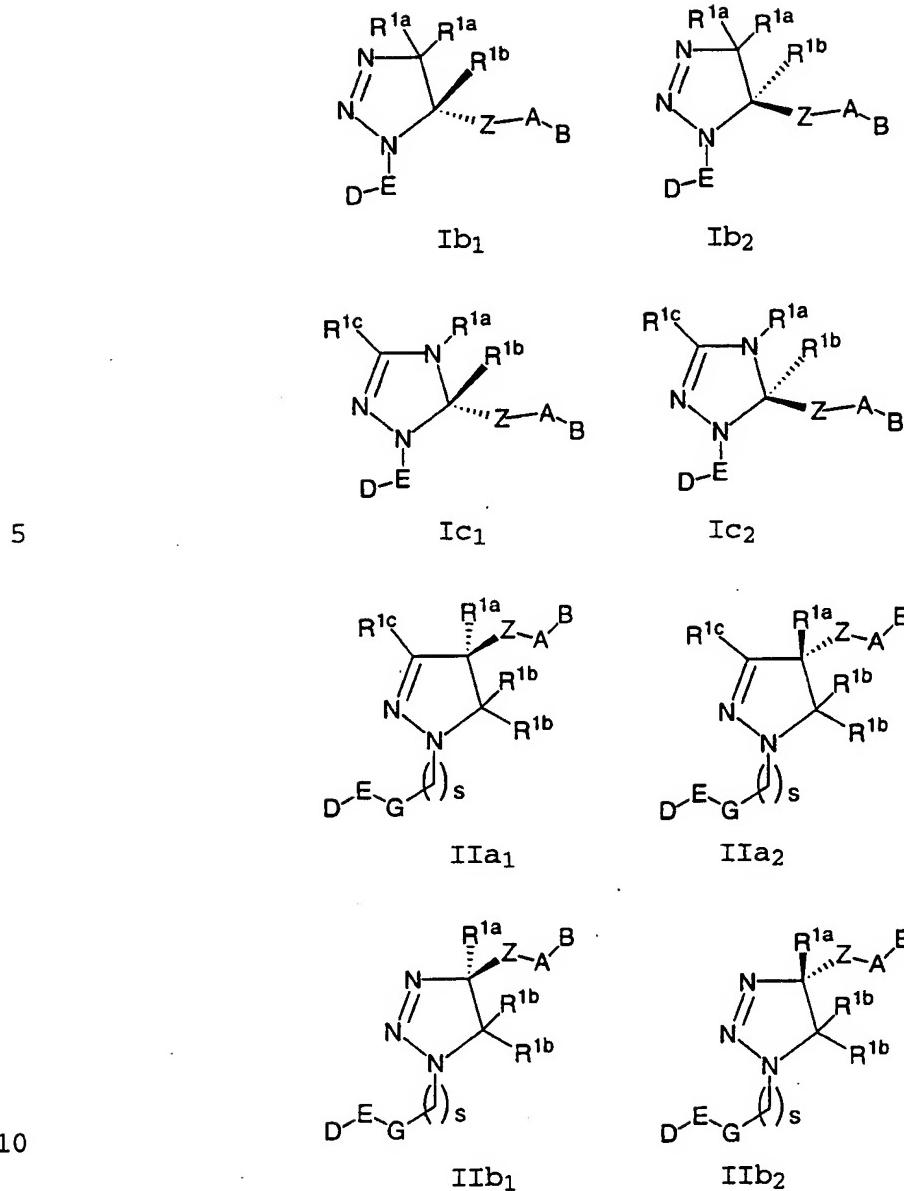
In Table E several methods of transforming a functional group Q into group D of Formula 1 are shown. While not all possible functional groups for Q and D are listed and the synthetic methods suggested are not comprehensive, Table E is meant to illustrate strategies and transformations available to a practitioner skilled in the art of organic synthesis for preparing compounds of Formula 1. In reaction 1 of Table E the transformation of a nitrile into an amidine by the Pinner methodology is shown; in reaction 2 the direct reduction of a nitrile by a hydride reducing agent to a methylene amine is illustrated. In reaction 3, the utility of a carboxylic acid, which may be readily derived from its ester or a nitrile if necessary, in the preparation of a methylene amine is shown. This synthetic route is exceptionally flexible because of the

several stable intermediates prepared en route to the final product. As outlined, formation of an activated analog, such as the mixed anhydride, allows for the mild reduction of the acid to the methylene alcohol, this may in turn be transformed 5 into a leaving group by sulfonylation or halogenation or protected with a suitable protecting group to be transformed later in the synthesis as the chemistry demands. Once the methylene alcohol is so activated, displacement by an efficient nitrogen nucleophile, such as azide anion, can again 10 provide another suitably stable analog, -the methylene azide- which may be used as a protected form of the methylene amine or transformed directly into the methylene amine group by reduction. Reaction 4 addresses the problem of appending the amine functionality directly through a bond to group E of 15 Formula 1. Once again, the carboxylic acid provides a convenient entre into this selection for group D. The well-known Curtius rearrangement is illustrated here; an activated acid analog can be used to form an acyl azide which upon thermal decomposition is rearranged to the corresponding 20 isocyanate. The isocyanate intermediate may then be captured as a stable carbamate by the addition of a suitable alcohol and further heating. This carbamate can be used as a stable protecting group for the amine or cleaved directly to the desired D. Alternatively, it may be convenient to quench the 25 isocyanate intermediate with water to give the amine directly.

One diastereomer of a compound of Formula I may display superior activity compared with the others. Thus, the following stereochemistries are considered to be a part of the present invention.

30





When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Steven D. Young, et al, *Antimicrobial Agents and Chemotherapy*, 1995, 2602-2605. A chiral compound of Formula I may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g., Andrew S. Thompson, et al, *Tet. lett.* 1995, 36, 8937-8940).

Other features of the invention will become apparent in the course of the following descriptions of exemplary

embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

### EXAMPLES

5

#### Examples 1 and 2

1-(3-Amidinophenyl)-5-[[[2'-methylsulfonyl-[1,1']-biphen-4-yl)-aminocarbonyl]-3-trifluoromethyl-pyrazoline and 1-(3-aminomethylphenyl)-5-[[[2'-methylsulfonyl-[1,1']-biphen-4-yl)-aminocarbonyl]-3-trifluoromethyl-pyrazoline

10

Part A: To a methanolic solution containing meta-cyanophenyl-hydrazine (2 g, 15.03 mmol) was added trifluoromethylacetaldehyde hydrate (1.74 g, 15.03 mmol). The reaction mixture was heated to gentle reflux overnight. Methanol was stripped off to afford yellow crystals of pure hydrazone (2.99g, 93%).  $^1\text{H}\text{NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 10.10 (bs, 1H), 7.33 (m, 2H), 7.10 (m, 2H) ppm; ESI (-ve) mass spectrum analysis m/z (relative intensity) 212 (M-H, 100).

20

Part B: NCS (1.02 g, 7.69 mmol) was added to a DMF (25 mL) solution of the compound prepared in part A (1.64 g, 7.69 mmol). The reaction mixture was stirred at room temperature over night, quenched with water (500 mL) and organics extracted with ethyl acetate (2x100 mL) dried ( $\text{MgSO}_4$ ) and evaporated to a reddish brown oil. The oil was redissolved in chloroform (25 mL) and to this solution was added ethyl acrylate (10 mL) followed by slow addition of triethylamine (0.81 mL, 5.75 mmol). The reaction mixture was refluxed for 18h cooled and quenched with dil. hydrochloric acid (1N, 20 mL). The organic layer was separated and evaporated to an oil. Chromatography on silica gel (7:3, Hexane:ethylacetate) afforded a colorless oil which solidified on standing (1.5 g, 62%).  $^1\text{H}\text{NMR}$  ( $\text{CDCl}_3$ ) $\delta$ : 7.40-7.22 (m, 4H), 4.89 (dd, J = 6.2 and 13.4Hz, 1H), 4.24 (q, 2H), 3.63-3.50 (dd, J = 1.9 and 13.2Hz, 1H), 3.38 (dd, J = 1.9 and 14Hz, 1H), 1.23 (t, 3H) ppm; ESI mass spectrum analysis m/z (relative intensity) 312 (M+H, 100).

Part C: The product from part B was treated with 2'-methylsulfonyl-4-amino-[1,1']biphenyl under Weinreb conditions (trimethylaluminum in dichloromethane) to afford pure coupled  
5 product (oil) after silica gel column chromatography (hexane:ethyl acetate 7:3).  $^1\text{H}\text{NMR}(\text{CDCl}_3)\delta:$  8.40 (bs, 1H), 8.17 (dd, J = 1.1 and 7.8Hz, 1H), 7.65-7.25 (m, 11H), 4.90 (m, 1H), 3.78 (m, 1H), 3.38 (dd, J = 1.5 and 8.1Hz, 1H), 2.69 s, 3H); ESI (-ve) mass spectrum analysis m/z (rel. intensity) 511 (M-H, 100).

Part D: The product from part C was subjected to the Pinner amidine reaction sequence (HCl/MeOH followed by ammonium carbonate in methanol), purified via standard HPLC  
15 purification, lyophilization to afford (40% yield) of Example 1 as colorless crystals.  $^1\text{H}\text{NMR}(\text{DMSO}_6)\delta:$  9.36 (bs, 1.5H), 9.00 (bs, 1.5Hz), 8.06 (d, J = 7.7Hz, 1H), 7.53-7.78 (m, 6H), 7.35 (d, J = 8.1Hz, 3H), 7.27 (d, J = 8.0Hz, 1H), 7.17 (d, J = 8.5Hz, 1H), 5.33 (dd, J = 6.2 and 13.2Hz, 1H), 3.76 (t, 1H), 3.40 (d, J = 3.1Hz, 1H), 2.84(s, 3H) ppm; ESI (+ve) mass spectrum analysis m/z (relative intensity) 530 (M+H, 100).

Additionally, the compound form Part C was subjected to reduction using 10% Pd/C in an acidic medium (methanol/acetic acid). Purification via standard HPLC techniques and lyophilization afforded the benzylamine (10% yield).  
 $^1\text{H}\text{NMR}(\text{DMSO}_6)\delta:$  8.07 (bs, 2H), 8.01 (d, J = 8Hz, 1H), 7.70 (m, 1H), 7.59 (m, 3H), 7.28 (m, 4H), 6.95 (d, J = 8Hz, 1H), 6.83 (dd, J = 1/5 and 8Hz, 1H), 6.40 (bs, 2H), 5.22 (dd, J = 6.5 and 13Hz, 1H), 4.00 (m, 1H), 3.71 (m, 1H), 3.34 (dd, J = 1.5 and 8Hz, 1H), 2.84 (s, 3H) ppm; ESI mass spectrum analysis m/z (relative intensity) 517 (M+H, 100).

The following tables contain representative examples of  
35 the present invention. Each entry in each table is intended to be paired with each formulae at the start of the table. For example, in Table 1, example 1 is intended to be paired

with each of formulae a-ttt and in Table 2, example 1 is intended to be paired with each of formulae a-ss.

The following groups are intended for group A in the following tables.

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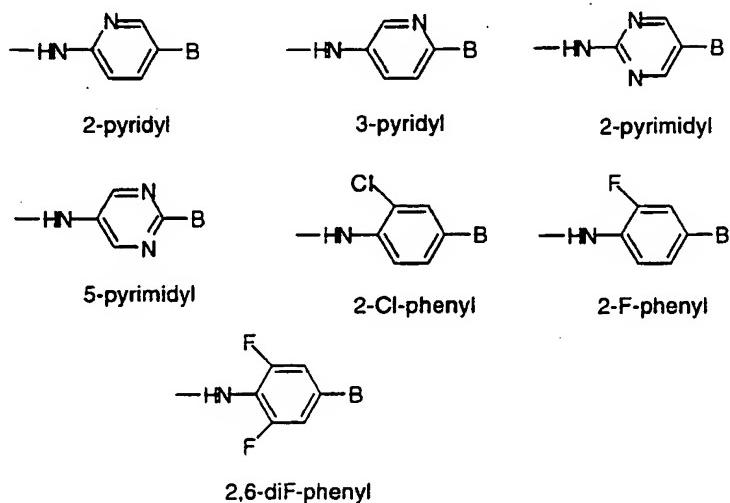
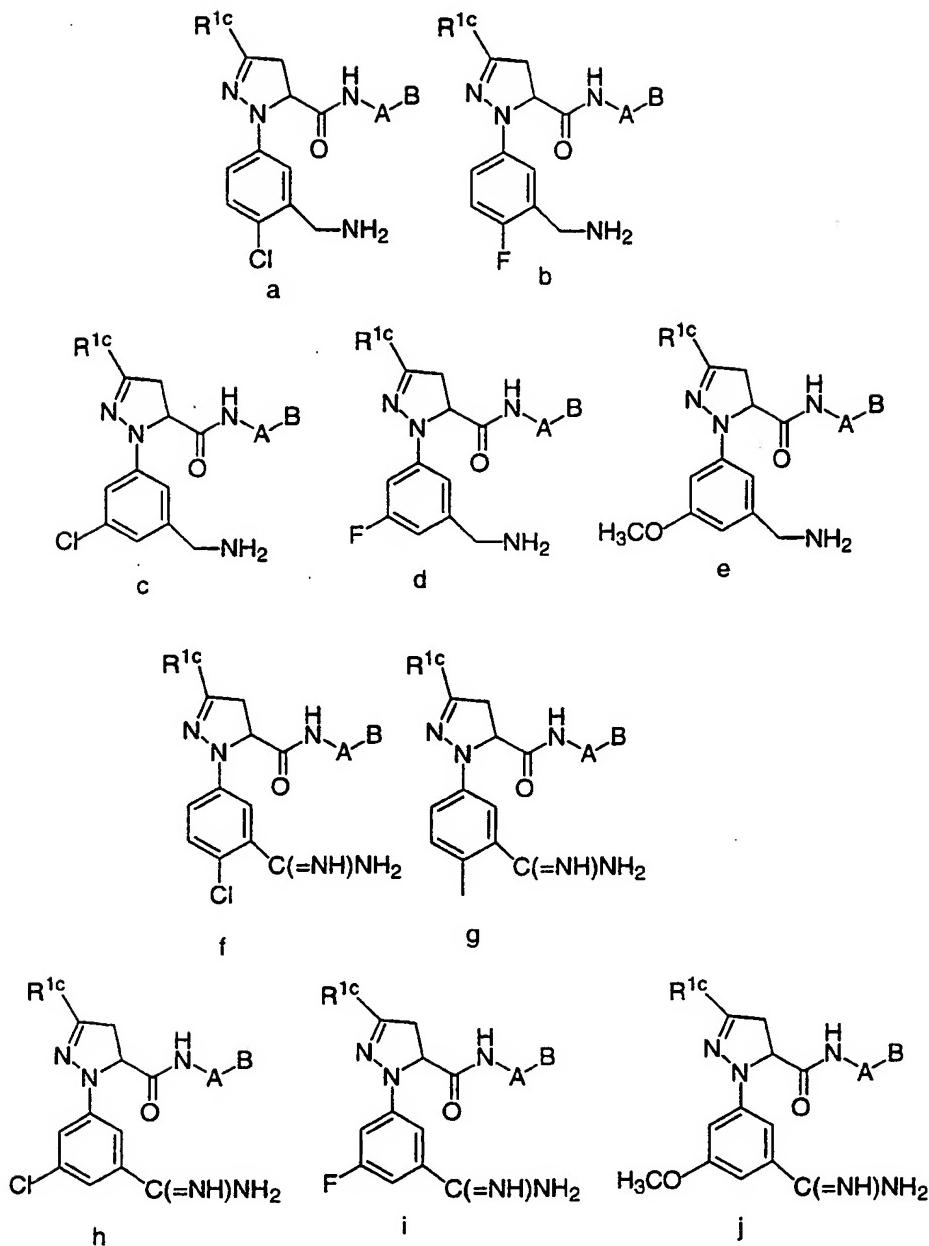
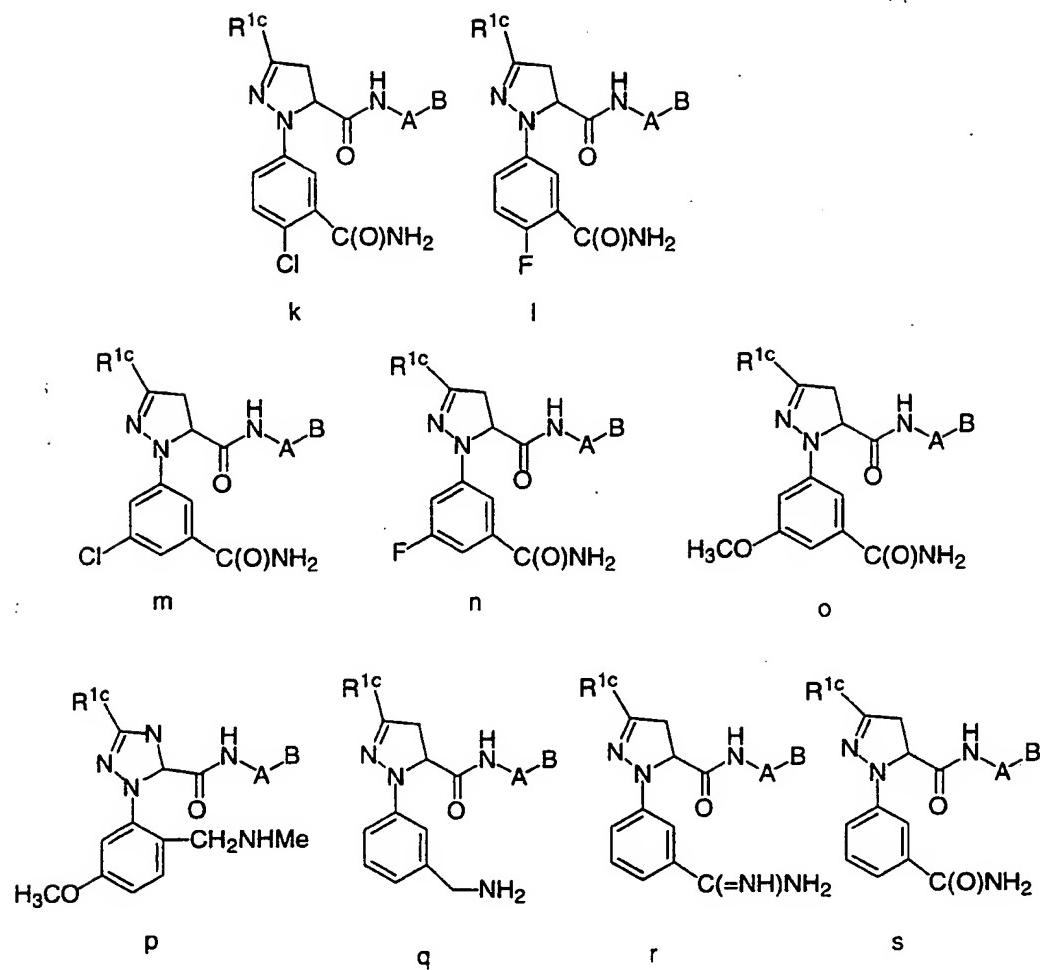
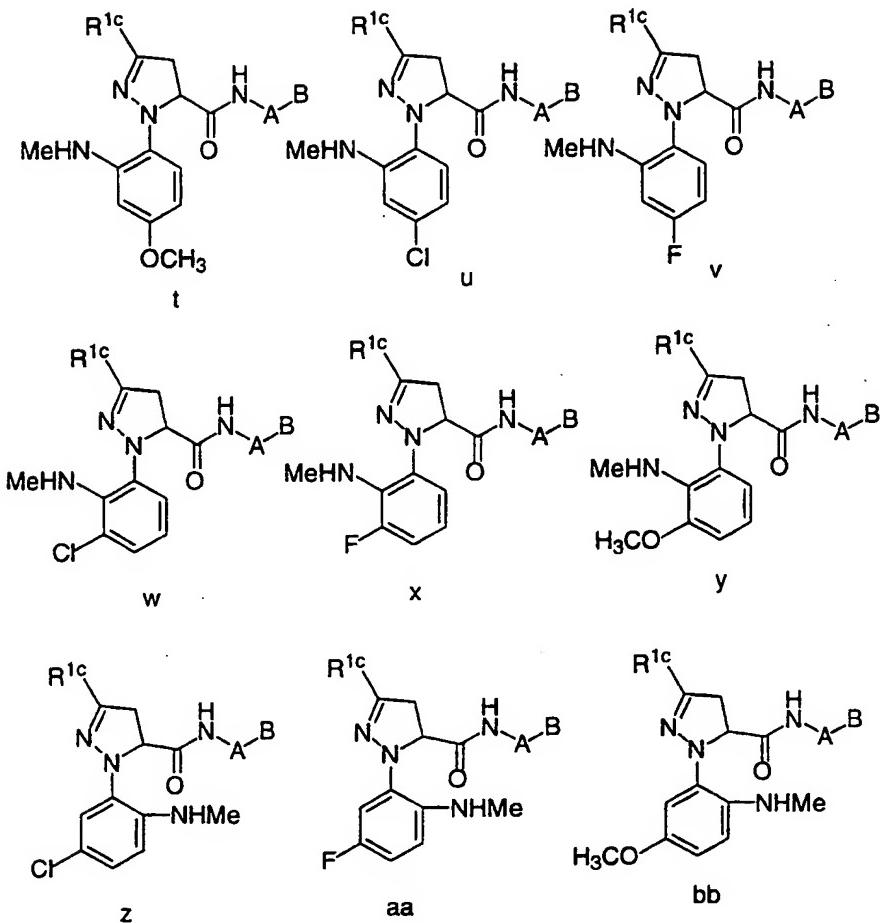


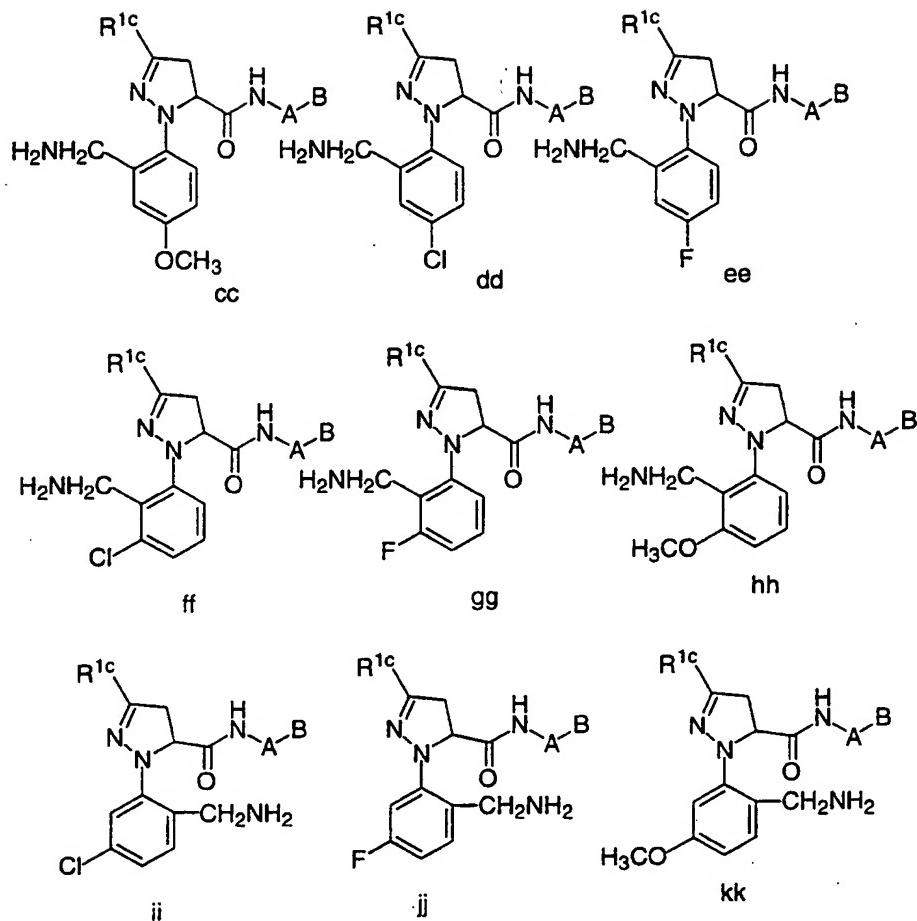
Table 1

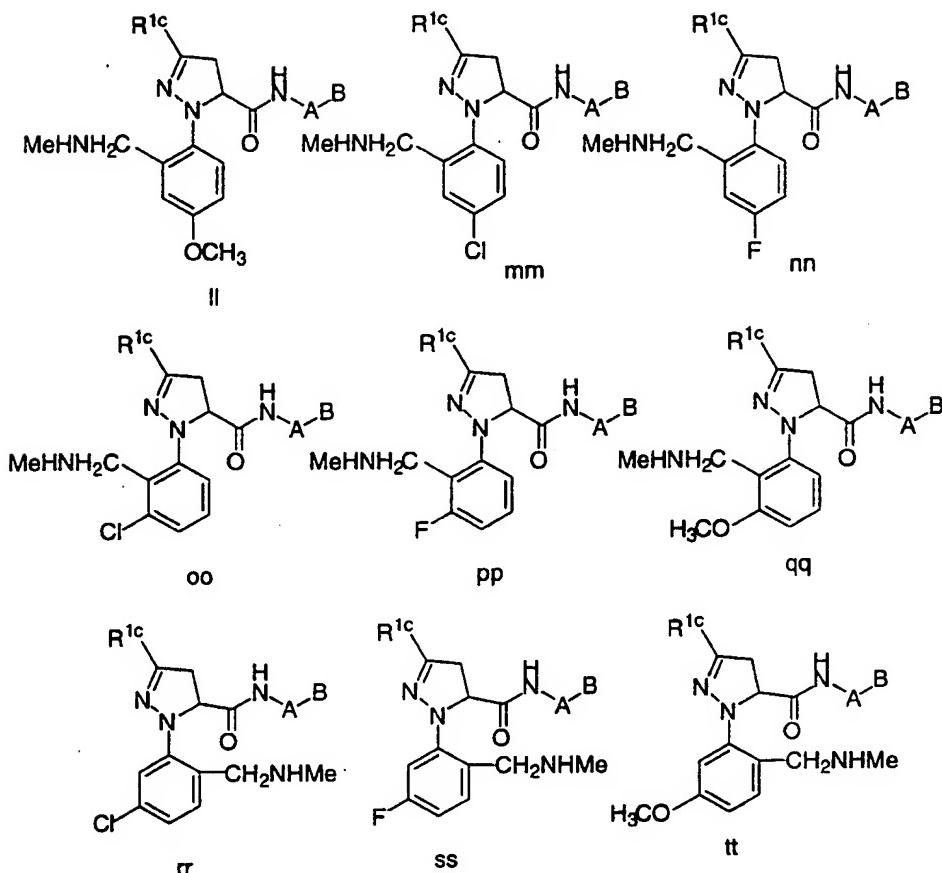


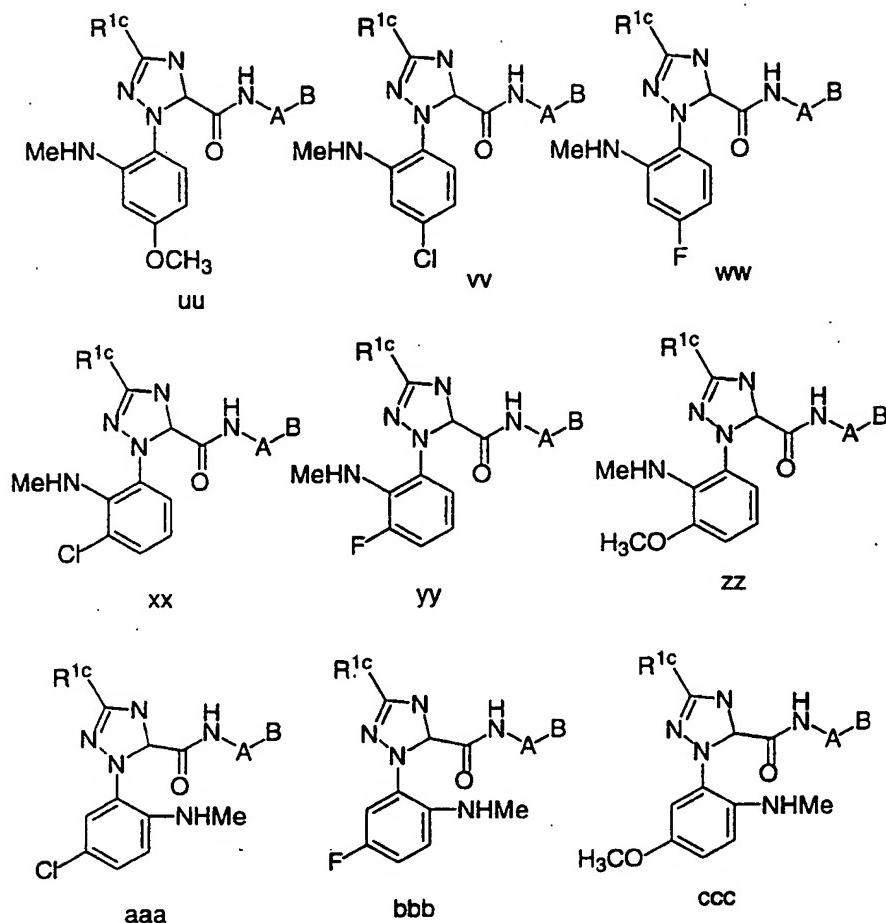
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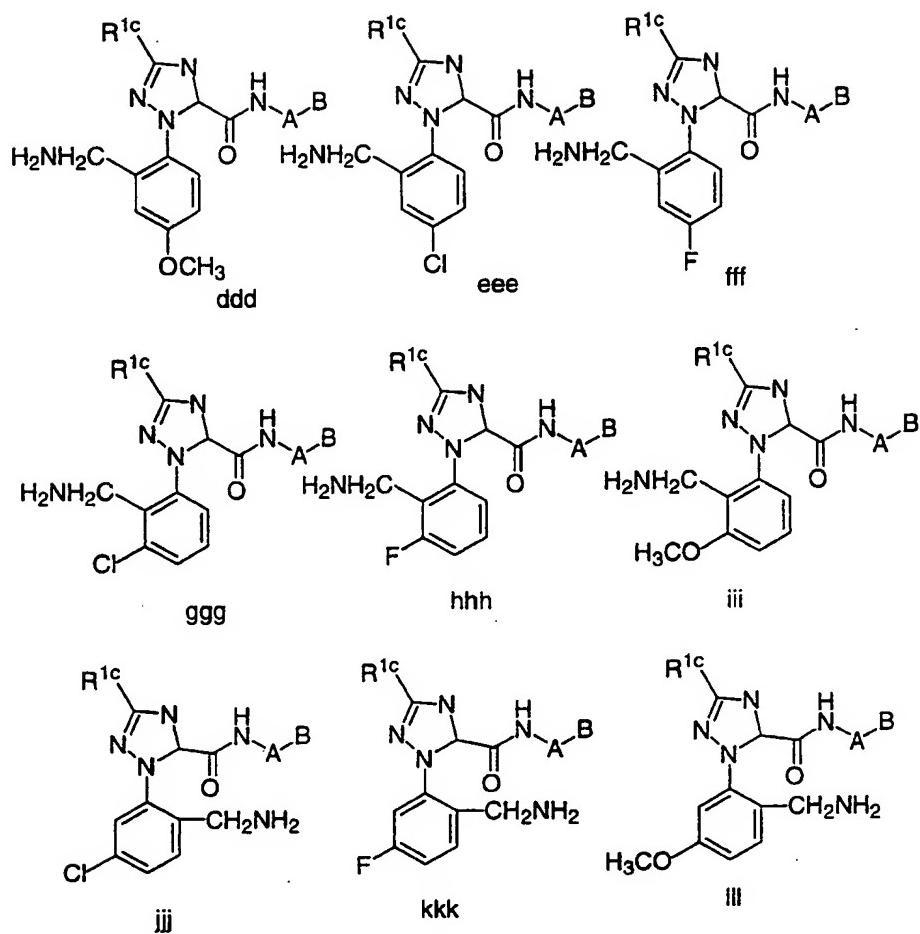


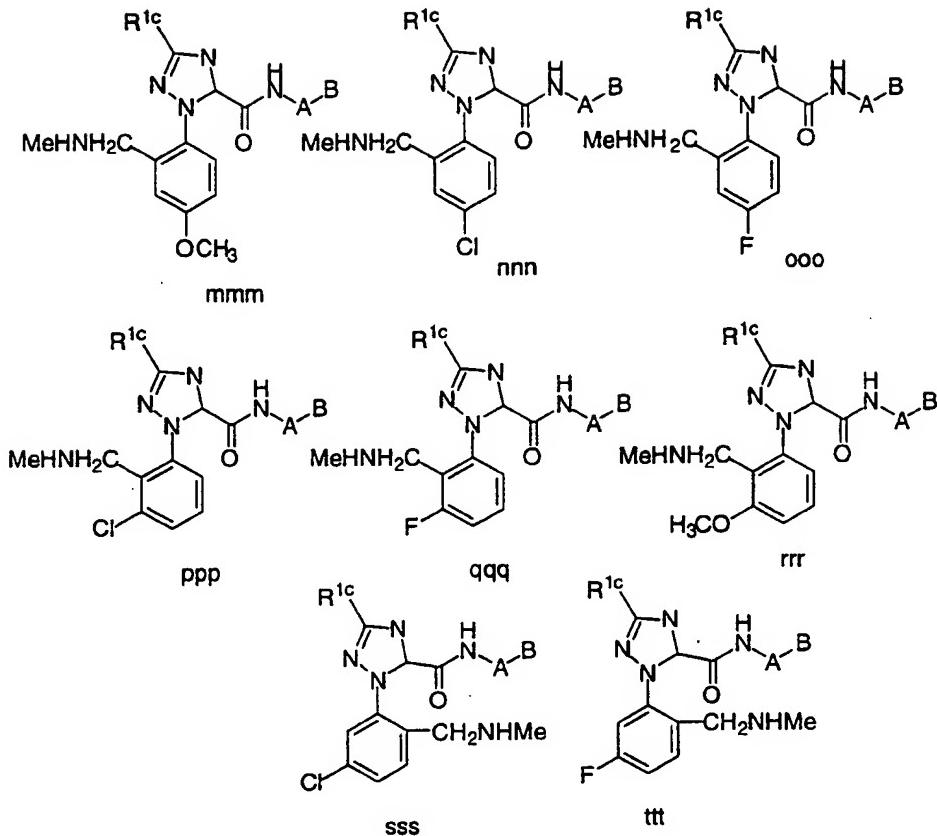












Ex #	R <sup>1c</sup>	A	B
1	CH <sub>3</sub>	phenyl	2-(aminosulfonyl)phenyl
2	CH <sub>3</sub>	phenyl	2-(methylaminosulfonyl)phenyl
3	CH <sub>3</sub>	phenyl	1-pyrrolidinocarbonyl
4	CH <sub>3</sub>	phenyl	2-(methylsulfonyl)phenyl
5	CH <sub>3</sub>	phenyl	4-morpholino
6	CH <sub>3</sub>	phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
7	CH <sub>3</sub>	phenyl	4-morpholinocarbonyl
8	CH <sub>3</sub>	phenyl	2-methyl-1-imidazolyl
9	CH <sub>3</sub>	phenyl	5-methyl-1-imidazolyl
10	CH <sub>3</sub>	phenyl	2-methylsulfonyl-1-imidazolyl
11	CH <sub>3</sub>	2-pyridyl	2-(aminosulfonyl)phenyl
12	CH <sub>3</sub>	2-pyridyl	2-(methylaminosulfonyl)phenyl
13	CH <sub>3</sub>	2-pyridyl	1-pyrrolidinocarbonyl
14	CH <sub>3</sub>	2-pyridyl	2-(methylsulfonyl)phenyl
15	CH <sub>3</sub>	2-pyridyl	4-morpholino
16	CH <sub>3</sub>	2-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
17	CH <sub>3</sub>	2-pyridyl	4-morpholinocarbonyl

18	CH <sub>3</sub>	2-pyridyl	2-methyl-1-imidazolyl
19	CH <sub>3</sub>	2-pyridyl	5-methyl-1-imidazolyl
20	CH <sub>3</sub>	2-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
21	CH <sub>3</sub>	3-pyridyl	2-(aminosulfonyl)phenyl
22	CH <sub>3</sub>	3-pyridyl	2-(methylaminosulfonyl)phenyl
23	CH <sub>3</sub>	3-pyridyl	1-pyrrolidinocarbonyl
24	CH <sub>3</sub>	3-pyridyl	2-(methylsulfonyl)phenyl
25	CH <sub>3</sub>	3-pyridyl	4-morpholino
26	CH <sub>3</sub>	3-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
27	CH <sub>3</sub>	3-pyridyl	4-morpholinocarbonyl
28	CH <sub>3</sub>	3-pyridyl	2-methyl-1-imidazolyl
29	CH <sub>3</sub>	3-pyridyl	5-methyl-1-imidazolyl
30	CH <sub>3</sub>	3-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
31	CH <sub>3</sub>	2-pyrimidyl	2-(aminosulfonyl)phenyl
32	CH <sub>3</sub>	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
33	CH <sub>3</sub>	2-pyrimidyl	1-pyrrolidinocarbonyl
34	CH <sub>3</sub>	2-pyrimidyl	2-(methylsulfonyl)phenyl
35	CH <sub>3</sub>	2-pyrimidyl	4-morpholino
36	CH <sub>3</sub>	2-pyrimidyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
37	CH <sub>3</sub>	2-pyrimidyl	4-morpholinocarbonyl
38	CH <sub>3</sub>	2-pyrimidyl	2-methyl-1-imidazolyl
39	CH <sub>3</sub>	2-pyrimidyl	5-methyl-1-imidazolyl
40	CH <sub>3</sub>	2-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
41	CH <sub>3</sub>	5-pyrimidyl	2-(aminosulfonyl)phenyl
42	CH <sub>3</sub>	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
43	CH <sub>3</sub>	5-pyrimidyl	1-pyrrolidinocarbonyl
44	CH <sub>3</sub>	5-pyrimidyl	2-(methylsulfonyl)phenyl
45	CH <sub>3</sub>	5-pyrimidyl	4-morpholino
46	CH <sub>3</sub>	5-pyrimidyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
47	CH <sub>3</sub>	5-pyrimidyl	4-morpholinocarbonyl
48	CH <sub>3</sub>	5-pyrimidyl	2-methyl-1-imidazolyl
49	CH <sub>3</sub>	5-pyrimidyl	5-methyl-1-imidazolyl
50	CH <sub>3</sub>	5-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
51	CH <sub>3</sub>	2-Cl-phenyl	2-(aminosulfonyl)phenyl
52	CH <sub>3</sub>	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
53	CH <sub>3</sub>	2-Cl-phenyl	1-pyrrolidinocarbonyl
54	CH <sub>3</sub>	2-Cl-phenyl	2-(methylsulfonyl)phenyl

55	CH <sub>3</sub>	2-Cl-phenyl	4-morpholino
56	CH <sub>3</sub>	2-Cl-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
57	CH <sub>3</sub>	2-Cl-phenyl	4-morpholinocarbonyl
58	CH <sub>3</sub>	2-Cl-phenyl	2-methyl-1-imidazolyl
59	CH <sub>3</sub>	2-Cl-phenyl	5-methyl-1-imidazolyl
60	CH <sub>3</sub>	2-Cl-phenyl	2-methylsulfonyl-1-imidazolyl
61	CH <sub>3</sub>	2-F-phenyl	2-(aminosulfonyl)phenyl
62	CH <sub>3</sub>	2-F-phenyl	2-(methylaminosulfonyl)phenyl
63	CH <sub>3</sub>	2-F-phenyl	1-pyrrolidinocarbonyl
64	CH <sub>3</sub>	2-F-phenyl	2-(methylsulfonyl)phenyl
65	CH <sub>3</sub>	2-F-phenyl	4-morpholino
66	CH <sub>3</sub>	2-F-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
67	CH <sub>3</sub>	2-F-phenyl	4-morpholinocarbonyl
68	CH <sub>3</sub>	2-F-phenyl	2-methyl-1-imidazolyl
69	CH <sub>3</sub>	2-F-phenyl	5-methyl-1-imidazolyl
70	CH <sub>3</sub>	2-F-phenyl	2-methylsulfonyl-1-imidazolyl
71	CH <sub>3</sub>	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
72	CH <sub>3</sub>	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
73	CH <sub>3</sub>	2,6-diF-phenyl	1-pyrrolidinocarbonyl
74	CH <sub>3</sub>	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
75	CH <sub>3</sub>	2,6-diF-phenyl	4-morpholino
76	CH <sub>3</sub>	2,6-diF-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
77	CH <sub>3</sub>	2,6-diF-phenyl	4-morpholinocarbonyl
78	CH <sub>3</sub>	2,6-diF-phenyl	2-methyl-1-imidazolyl
79	CH <sub>3</sub>	2,6-diF-phenyl	5-methyl-1-imidazolyl
80	CH <sub>3</sub>	2,6-diF-phenyl	2-methylsulfonyl-1-imidazolyl
81	CH <sub>2</sub> CH <sub>3</sub>	phenyl	2-(aminosulfonyl)phenyl
82	CH <sub>2</sub> CH <sub>3</sub>	phenyl	2-(methylaminosulfonyl)phenyl
83	CH <sub>2</sub> CH <sub>3</sub>	phenyl	1-pyrrolidinocarbonyl
84	CH <sub>2</sub> CH <sub>3</sub>	phenyl	2-(methylsulfonyl)phenyl
85	CH <sub>2</sub> CH <sub>3</sub>	phenyl	4-morpholino
86	CH <sub>2</sub> CH <sub>3</sub>	phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
87	CH <sub>2</sub> CH <sub>3</sub>	phenyl	4-morpholinocarbonyl
88	CH <sub>2</sub> CH <sub>3</sub>	phenyl	2-methyl-1-imidazolyl
89	CH <sub>2</sub> CH <sub>3</sub>	phenyl	5-methyl-1-imidazolyl
90	CH <sub>2</sub> CH <sub>3</sub>	phenyl	2-methylsulfonyl-1-imidazolyl
91	CH <sub>2</sub> CH <sub>3</sub>	2-pyridyl	2-(aminosulfonyl)phenyl

92	CH <sub>2</sub> CH <sub>3</sub>	2-pyridyl	2-(methylaminosulfonyl)phenyl
93	CH <sub>2</sub> CH <sub>3</sub>	2-pyridyl	1-pyrrolidinocarbonyl
94	CH <sub>2</sub> CH <sub>3</sub>	2-pyridyl	2-(methylsulfonyl)phenyl
95	CH <sub>2</sub> CH <sub>3</sub>	2-pyridyl	4-morpholino
96	CH <sub>2</sub> CH <sub>3</sub>	2-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
97	CH <sub>2</sub> CH <sub>3</sub>	2-pyridyl	4-morpholinocarbonyl
98	CH <sub>2</sub> CH <sub>3</sub>	2-pyridyl	2-methyl-1-imidazolyl
99	CH <sub>2</sub> CH <sub>3</sub>	2-pyridyl	5-methyl-1-imidazolyl
100	CH <sub>2</sub> CH <sub>3</sub>	2-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
101	CH <sub>2</sub> CH <sub>3</sub>	3-pyridyl	2-(aminosulfonyl)phenyl
102	CH <sub>2</sub> CH <sub>3</sub>	3-pyridyl	2-(methylaminosulfonyl)phenyl
103	CH <sub>2</sub> CH <sub>3</sub>	3-pyridyl	1-pyrrolidinocarbonyl
104	CH <sub>2</sub> CH <sub>3</sub>	3-pyridyl	2-(methylsulfonyl)phenyl
105	CH <sub>2</sub> CH <sub>3</sub>	3-pyridyl	4-morpholino
106	CH <sub>2</sub> CH <sub>3</sub>	3-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
107	CH <sub>2</sub> CH <sub>3</sub>	3-pyridyl	4-morpholinocarbonyl
108	CH <sub>2</sub> CH <sub>3</sub>	3-pyridyl	2-methyl-1-imidazolyl
109	CH <sub>2</sub> CH <sub>3</sub>	3-pyridyl	5-methyl-1-imidazolyl
110	CH <sub>2</sub> CH <sub>3</sub>	3-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
111	CH <sub>2</sub> CH <sub>3</sub>	2-pyrimidyl	2-(aminosulfonyl)phenyl
112	CH <sub>2</sub> CH <sub>3</sub>	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
113	CH <sub>2</sub> CH <sub>3</sub>	2-pyrimidyl	1-pyrrolidinocarbonyl
114	CH <sub>2</sub> CH <sub>3</sub>	2-pyrimidyl	2-(methylsulfonyl)phenyl
115	CH <sub>2</sub> CH <sub>3</sub>	2-pyrimidyl	4-morpholino
116	CH <sub>2</sub> CH <sub>3</sub>	2-pyrimidyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
117	CH <sub>2</sub> CH <sub>3</sub>	2-pyrimidyl	4-morpholinocarbonyl
118	CH <sub>2</sub> CH <sub>3</sub>	2-pyrimidyl	2-methyl-1-imidazolyl
119	CH <sub>2</sub> CH <sub>3</sub>	2-pyrimidyl	5-methyl-1-imidazolyl
120	CH <sub>2</sub> CH <sub>3</sub>	2-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
121	CH <sub>2</sub> CH <sub>3</sub>	5-pyrimidyl	2-(aminosulfonyl)phenyl
122	CH <sub>2</sub> CH <sub>3</sub>	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
123	CH <sub>2</sub> CH <sub>3</sub>	5-pyrimidyl	1-pyrrolidinocarbonyl
124	CH <sub>2</sub> CH <sub>3</sub>	5-pyrimidyl	2-(methylsulfonyl)phenyl
125	CH <sub>2</sub> CH <sub>3</sub>	5-pyrimidyl	4-morpholino
126	CH <sub>2</sub> CH <sub>3</sub>	5-pyrimidyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
127	CH <sub>2</sub> CH <sub>3</sub>	5-pyrimidyl	4-morpholinocarbonyl
128	CH <sub>2</sub> CH <sub>3</sub>	5-pyrimidyl	2-methyl-1-imidazolyl

129	CH <sub>2</sub> CH <sub>3</sub>	5-pyrimidyl	5-methyl-1-imidazolyl
130	CH <sub>2</sub> CH <sub>3</sub>	5-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
131	CH <sub>2</sub> CH <sub>3</sub>	2-Cl-phenyl	2-(aminosulfonyl)phenyl
132	CH <sub>2</sub> CH <sub>3</sub>	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
133	CH <sub>2</sub> CH <sub>3</sub>	2-Cl-phenyl	1-pyrrolidinocarbonyl
134	CH <sub>2</sub> CH <sub>3</sub>	2-Cl-phenyl	2-(methylsulfonyl)phenyl
135	CH <sub>2</sub> CH <sub>3</sub>	2-Cl-phenyl	4-morpholino
136	CH <sub>2</sub> CH <sub>3</sub>	2-Cl-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
137	CH <sub>2</sub> CH <sub>3</sub>	2-Cl-phenyl	4-morpholinocarbonyl
138	CH <sub>2</sub> CH <sub>3</sub>	2-Cl-phenyl	2-methyl-1-imidazolyl
139	CH <sub>2</sub> CH <sub>3</sub>	2-Cl-phenyl	5-methyl-1-imidazolyl
140	CH <sub>2</sub> CH <sub>3</sub>	2-Cl-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
141	CH <sub>2</sub> CH <sub>3</sub>	2-F-phenyl	2-(aminosulfonyl)phenyl
142	CH <sub>2</sub> CH <sub>3</sub>	2-F-phenyl	2-(methylaminosulfonyl)phenyl
143	CH <sub>2</sub> CH <sub>3</sub>	2-F-phenyl	1-pyrrolidinocarbonyl
144	CH <sub>2</sub> CH <sub>3</sub>	2-F-phenyl	2-(methylsulfonyl)phenyl
145	CH <sub>2</sub> CH <sub>3</sub>	2-F-phenyl	4-morpholino
146	CH <sub>2</sub> CH <sub>3</sub>	2-F-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
147	CH <sub>2</sub> CH <sub>3</sub>	2-F-phenyl	4-morpholinocarbonyl
148	CH <sub>2</sub> CH <sub>3</sub>	2-F-phenyl	2-methyl-1-imidazolyl
149	CH <sub>2</sub> CH <sub>3</sub>	2-F-phenyl	5-methyl-1-imidazolyl
150	CH <sub>2</sub> CH <sub>3</sub>	2-F-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
151	CH <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
152	CH <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
153	CH <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	1-pyrrolidinocarbonyl
154	CH <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
155	CH <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	4-morpholino
156	CH <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
157	CH <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	4-morpholinocarbonyl
158	CH <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	2-methyl-1-imidazolyl
159	CH <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	5-methyl-1-imidazolyl
160	CH <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
161	CF <sub>3</sub>	phenyl	2-(aminosulfonyl)phenyl
162	CF <sub>3</sub>	phenyl	2-(methylaminosulfonyl)phenyl
163	CF <sub>3</sub>	phenyl	1-pyrrolidinocarbonyl
164	CF <sub>3</sub>	phenyl	2-(methylsulfonyl)phenyl
165	CF <sub>3</sub>	phenyl	4-morpholino

166	$\text{CF}_3$	phenyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
167	$\text{CF}_3$	phenyl	4-morpholinocarbonyl
168	$\text{CF}_3$	phenyl	2-methyl-1-imidazolyl
169	$\text{CF}_3$	phenyl	5-methyl-1-imidazolyl
170	$\text{CF}_3$	phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
171	$\text{CF}_3$	2-pyridyl	2-(aminosulfonyl)phenyl
172	$\text{CF}_3$	2-pyridyl	2-(methylaminosulfonyl)phenyl
173	$\text{CF}_3$	2-pyridyl	1-pyrrolidinocarbonyl
174	$\text{CF}_3$	2-pyridyl	2-(methylsulfonyl)phenyl
175	$\text{CF}_3$	2-pyridyl	4-morpholino
176	$\text{CF}_3$	2-pyridyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
177	$\text{CF}_3$	2-pyridyl	4-morpholinocarbonyl
178	$\text{CF}_3$	2-pyridyl	2-methyl-1-imidazolyl
179	$\text{CF}_3$	2-pyridyl	5-methyl-1-imidazolyl
180	$\text{CF}_3$	2-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
181	$\text{CF}_3$	3-pyridyl	2-(aminosulfonyl)phenyl
182	$\text{CF}_3$	3-pyridyl	2-(methylaminosulfonyl)phenyl
183	$\text{CF}_3$	3-pyridyl	1-pyrrolidinocarbonyl
184	$\text{CF}_3$	3-pyridyl	2-(methylsulfonyl)phenyl
185	$\text{CF}_3$	3-pyridyl	4-morpholino
186	$\text{CF}_3$	3-pyridyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
187	$\text{CF}_3$	3-pyridyl	4-morpholinocarbonyl
188	$\text{CF}_3$	3-pyridyl	2-methyl-1-imidazolyl
189	$\text{CF}_3$	3-pyridyl	5-methyl-1-imidazolyl
190	$\text{CF}_3$	3-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
191	$\text{CF}_3$	2-pyrimidyl	2-(aminosulfonyl)phenyl
192	$\text{CF}_3$	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
193	$\text{CF}_3$	2-pyrimidyl	1-pyrrolidinocarbonyl
194	$\text{CF}_3$	2-pyrimidyl	2-(methylsulfonyl)phenyl
195	$\text{CF}_3$	2-pyrimidyl	4-morpholino
196	$\text{CF}_3$	2-pyrimidyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
197	$\text{CF}_3$	2-pyrimidyl	4-morpholinocarbonyl
198	$\text{CF}_3$	2-pyrimidyl	2-methyl-1-imidazolyl
199	$\text{CF}_3$	2-pyrimidyl	5-methyl-1-imidazolyl
200	$\text{CF}_3$	2-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
201	$\text{CF}_3$	5-pyrimidyl	2-(aminosulfonyl)phenyl
202	$\text{CF}_3$	5-pyrimidyl	2-(methylaminosulfonyl)phenyl

203	CF <sub>3</sub>	5-pyrimidyl	1-pyrrolidinocarbonyl
204	CF <sub>3</sub>	5-pyrimidyl	2-(methylsulfonyl)phenyl
205	CF <sub>3</sub>	5-pyrimidyl	4-morpholino
206	CF <sub>3</sub>	5-pyrimidyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
207	CF <sub>3</sub>	5-pyrimidyl	4-morpholinocarbonyl
208	CF <sub>3</sub>	5-pyrimidyl	2-methyl-1-imidazolyl
209	CF <sub>3</sub>	5-pyrimidyl	5-methyl-1-imidazolyl
210	CF <sub>3</sub>	5-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
211	CF <sub>3</sub>	2-Cl-phenyl	2-(aminosulfonyl)phenyl
212	CF <sub>3</sub>	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
213	CF <sub>3</sub>	2-Cl-phenyl	1-pyrrolidinocarbonyl
214	CF <sub>3</sub>	2-Cl-phenyl	2-(methylsulfonyl)phenyl
215	CF <sub>3</sub>	2-Cl-phenyl	4-morpholino
216	CF <sub>3</sub>	2-Cl-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
217	CF <sub>3</sub>	2-Cl-phenyl	4-morpholinocarbonyl
218	CF <sub>3</sub>	2-Cl-phenyl	2-methyl-1-imidazolyl
219	CF <sub>3</sub>	2-Cl-phenyl	5-methyl-1-imidazolyl
220	CF <sub>3</sub>	2-Cl-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
221	CF <sub>3</sub>	2-F-phenyl	2-(aminosulfonyl)phenyl
222	CF <sub>3</sub>	2-F-phenyl	2-(methylaminosulfonyl)phenyl
223	CF <sub>3</sub>	2-F-phenyl	1-pyrrolidinocarbonyl
224	CF <sub>3</sub>	2-F-phenyl	2-(methylsulfonyl)phenyl
225	CF <sub>3</sub>	2-F-phenyl	4-morpholino
226	CF <sub>3</sub>	2-F-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
227	CF <sub>3</sub>	2-F-phenyl	4-morpholinocarbonyl
228	CF <sub>3</sub>	2-F-phenyl	2-methyl-1-imidazolyl
229	CF <sub>3</sub>	2-F-phenyl	5-methyl-1-imidazolyl
230	CF <sub>3</sub>	2-F-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
231	CF <sub>3</sub>	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
232	CF <sub>3</sub>	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
233	CF <sub>3</sub>	2,6-diF-phenyl	1-pyrrolidinocarbonyl
234	CF <sub>3</sub>	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
235	CF <sub>3</sub>	2,6-diF-phenyl	4-morpholino
236	CF <sub>3</sub>	2,6-diF-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
237	CF <sub>3</sub>	2,6-diF-phenyl	4-morpholinocarbonyl
238	CF <sub>3</sub>	2,6-diF-phenyl	2-methyl-1-imidazolyl
239	CF <sub>3</sub>	2,6-diF-phenyl	5-methyl-1-imidazolyl

240	$\text{CF}_3$	2,6-diF-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
241	$\text{SCH}_3$	phenyl	2-(aminosulfonyl)phenyl
242	$\text{SCH}_3$	phenyl	2-(methylaminosulfonyl)phenyl
243	$\text{SCH}_3$	phenyl	1-pyrrolidinocarbonyl
244	$\text{SCH}_3$	phenyl	2-(methylsulfonyl)phenyl
245	$\text{SCH}_3$	phenyl	4-morpholino
246	$\text{SCH}_3$	phenyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
247	$\text{SCH}_3$	phenyl	4-morpholinocarbonyl
248	$\text{SCH}_3$	phenyl	2-methyl-1-imidazolyl
249	$\text{SCH}_3$	phenyl	5-methyl-1-imidazolyl
250	$\text{SCH}_3$	phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
251	$\text{SCH}_3$	2-pyridyl	2-(aminosulfonyl)phenyl
252	$\text{SCH}_3$	2-pyridyl	2-(methylaminosulfonyl)phenyl
253	$\text{SCH}_3$	2-pyridyl	1-pyrrolidinocarbonyl
254	$\text{SCH}_3$	2-pyridyl	2-(methylsulfonyl)phenyl
255	$\text{SCH}_3$	2-pyridyl	4-morpholino
256	$\text{SCH}_3$	2-pyridyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
257	$\text{SCH}_3$	2-pyridyl	4-morpholinocarbonyl
258	$\text{SCH}_3$	2-pyridyl	2-methyl-1-imidazolyl
259	$\text{SCH}_3$	2-pyridyl	5-methyl-1-imidazolyl
260	$\text{SCH}_3$	2-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
261	$\text{SCH}_3$	3-pyridyl	2-(aminosulfonyl)phenyl
262	$\text{SCH}_3$	3-pyridyl	2-(methylaminosulfonyl)phenyl
263	$\text{SCH}_3$	3-pyridyl	1-pyrrolidinocarbonyl
264	$\text{SCH}_3$	3-pyridyl	2-(methylsulfonyl)phenyl
265	$\text{SCH}_3$	3-pyridyl	4-morpholino
266	$\text{SCH}_3$	3-pyridyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
267	$\text{SCH}_3$	3-pyridyl	4-morpholinocarbonyl
268	$\text{SCH}_3$	3-pyridyl	2-methyl-1-imidazolyl
269	$\text{SCH}_3$	3-pyridyl	5-methyl-1-imidazolyl
270	$\text{SCH}_3$	3-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
271	$\text{SCH}_3$	2-pyrimidyl	2-(aminosulfonyl)phenyl
272	$\text{SCH}_3$	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
273	$\text{SCH}_3$	2-pyrimidyl	1-pyrrolidinocarbonyl
274	$\text{SCH}_3$	2-pyrimidyl	2-(methylsulfonyl)phenyl
275	$\text{SCH}_3$	2-pyrimidyl	4-morpholino
276	$\text{SCH}_3$	2-pyrimidyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl

277	SCH <sub>3</sub>	2-pyrimidyl	4-morpholinocarbonyl
278	SCH <sub>3</sub>	2-pyrimidyl	2-methyl-1-imidazolyl
279	SCH <sub>3</sub>	2-pyrimidyl	5-methyl-1-imidazolyl
280	SCH <sub>3</sub>	2-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
281	SCH <sub>3</sub>	5-pyrimidyl	2-(aminosulfonyl)phenyl
282	SCH <sub>3</sub>	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
283	SCH <sub>3</sub>	5-pyrimidyl	1-pyrrolidinocarbonyl
284	SCH <sub>3</sub>	5-pyrimidyl	2-(methylsulfonyl)phenyl
285	SCH <sub>3</sub>	5-pyrimidyl	4-morpholino
286	SCH <sub>3</sub>	5-pyrimidyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
287	SCH <sub>3</sub>	5-pyrimidyl	4-morpholinocarbonyl
288	SCH <sub>3</sub>	5-pyrimidyl	2-methyl-1-imidazolyl
289	SCH <sub>3</sub>	5-pyrimidyl	5-methyl-1-imidazolyl
290	SCH <sub>3</sub>	5-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
291	SCH <sub>3</sub>	2-Cl-phenyl	2-(aminosulfonyl)phenyl
292	SCH <sub>3</sub>	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
293	SCH <sub>3</sub>	2-Cl-phenyl	1-pyrrolidinocarbonyl
294	SCH <sub>3</sub>	2-Cl-phenyl	2-(methylsulfonyl)phenyl
295	SCH <sub>3</sub>	2-Cl-phenyl	4-morpholino
296	SCH <sub>3</sub>	2-Cl-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
297	SCH <sub>3</sub>	2-Cl-phenyl	4-morpholinocarbonyl
298	SCH <sub>3</sub>	2-Cl-phenyl	2-methyl-1-imidazolyl
299	SCH <sub>3</sub>	2-Cl-phenyl	5-methyl-1-imidazolyl
300	SCH <sub>3</sub>	2-Cl-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
301	SCH <sub>3</sub>	2-F-phenyl	2-(aminosulfonyl)phenyl
302	SCH <sub>3</sub>	2-F-phenyl	2-(methylaminosulfonyl)phenyl
303	SCH <sub>3</sub>	2-F-phenyl	1-pyrrolidinocarbonyl
304	SCH <sub>3</sub>	2-F-phenyl	2-(methylsulfonyl)phenyl
305	SCH <sub>3</sub>	2-F-phenyl	4-morpholino
306	SCH <sub>3</sub>	2-F-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
307	SCH <sub>3</sub>	2-F-phenyl	4-morpholinocarbonyl
308	SCH <sub>3</sub>	2-F-phenyl	2-methyl-1-imidazolyl
309	SCH <sub>3</sub>	2-F-phenyl	5-methyl-1-imidazolyl
310	SCH <sub>3</sub>	2-F-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
311	SCH <sub>3</sub>	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
312	SCH <sub>3</sub>	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
313	SCH <sub>3</sub>	2,6-diF-phenyl	1-pyrrolidinocarbonyl

314	SCH <sub>3</sub>	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
315	SCH <sub>3</sub>	2,6-diF-phenyl	4-morpholino
316	SCH <sub>3</sub>	2,6-diF-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
317	SCH <sub>3</sub>	2,6-diF-phenyl	4-morpholinocarbonyl
318	SCH <sub>3</sub>	2,6-diF-phenyl	2-methyl-1-imidazolyl
319	SCH <sub>3</sub>	2,6-diF-phenyl	5-methyl-1-imidazolyl
320	SCH <sub>3</sub>	2,6-diF-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
321	SOCH <sub>3</sub>	phenyl	2-(aminosulfonyl)phenyl
322	SOCH <sub>3</sub>	phenyl	2-(methylaminosulfonyl)phenyl
323	SOCH <sub>3</sub>	phenyl	1-pyrrolidinocarbonyl
324	SOCH <sub>3</sub>	phenyl	2-(methylsulfonyl)phenyl
325	SOCH <sub>3</sub>	phenyl	4-morpholino
326	SOCH <sub>3</sub>	phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
327	SOCH <sub>3</sub>	phenyl	4-morpholinocarbonyl
328	SOCH <sub>3</sub>	phenyl	2-methyl-1-imidazolyl
329	SOCH <sub>3</sub>	phenyl	5-methyl-1-imidazolyl
330	SOCH <sub>3</sub>	phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
331	SOCH <sub>3</sub>	2-pyridyl	2-(aminosulfonyl)phenyl
332	SOCH <sub>3</sub>	2-pyridyl	2-(methylaminosulfonyl)phenyl
333	SOCH <sub>3</sub>	2-pyridyl	1-pyrrolidinocarbonyl
334	SOCH <sub>3</sub>	2-pyridyl	2-(methylsulfonyl)phenyl
335	SOCH <sub>3</sub>	2-pyridyl	4-morpholino
336	SOCH <sub>3</sub>	2-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
337	SOCH <sub>3</sub>	2-pyridyl	4-morpholinocarbonyl
338	SOCH <sub>3</sub>	2-pyridyl	2-methyl-1-imidazolyl
339	SOCH <sub>3</sub>	2-pyridyl	5-methyl-1-imidazolyl
340	SOCH <sub>3</sub>	2-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
341	SOCH <sub>3</sub>	3-pyridyl	2-(aminosulfonyl)phenyl
342	SOCH <sub>3</sub>	3-pyridyl	2-(methylaminosulfonyl)phenyl
343	SOCH <sub>3</sub>	3-pyridyl	1-pyrrolidinocarbonyl
344	SOCH <sub>3</sub>	3-pyridyl	2-(methylsulfonyl)phenyl
345	SOCH <sub>3</sub>	3-pyridyl	4-morpholino
346	SOCH <sub>3</sub>	3-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
347	SOCH <sub>3</sub>	3-pyridyl	4-morpholinocarbonyl
348	SOCH <sub>3</sub>	3-pyridyl	2-methyl-1-imidazolyl
349	SOCH <sub>3</sub>	3-pyridyl	5-methyl-1-imidazolyl
350	SOCH <sub>3</sub>	3-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>

351	$\text{SOCH}_3$	2-pyrimidyl	2-(aminosulfonyl)phenyl
352	$\text{SOCH}_3$	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
353	$\text{SOCH}_3$	2-pyrimidyl	1-pyrrolidinocarbonyl
354	$\text{SOCH}_3$	2-pyrimidyl	2-(methylsulfonyl)phenyl
355	$\text{SOCH}_3$	2-pyrimidyl	4-morpholino
356	$\text{SOCH}_3$	2-pyrimidyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
357	$\text{SOCH}_3$	2-pyrimidyl	4-morpholinocarbonyl
358	$\text{SOCH}_3$	2-pyrimidyl	2-methyl-1-imidazolyl
359	$\text{SOCH}_3$	2-pyrimidyl	5-methyl-1-imidazolyl
360	$\text{SOCH}_3$	2-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
361	$\text{SOCH}_3$	5-pyrimidyl	2-(aminosulfonyl)phenyl
362	$\text{SOCH}_3$	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
363	$\text{SOCH}_3$	5-pyrimidyl	1-pyrrolidinocarbonyl
364	$\text{SOCH}_3$	5-pyrimidyl	2-(methylsulfonyl)phenyl
365	$\text{SOCH}_3$	5-pyrimidyl	4-morpholino
366	$\text{SOCH}_3$	5-pyrimidyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
367	$\text{SOCH}_3$	5-pyrimidyl	4-morpholinocarbonyl
368	$\text{SOCH}_3$	5-pyrimidyl	2-methyl-1-imidazolyl
369	$\text{SOCH}_3$	5-pyrimidyl	5-methyl-1-imidazolyl
370	$\text{SOCH}_3$	5-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
371	$\text{SOCH}_3$	2-Cl-phenyl	2-(aminosulfonyl)phenyl
372	$\text{SOCH}_3$	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
373	$\text{SOCH}_3$	2-Cl-phenyl	1-pyrrolidinocarbonyl
374	$\text{SOCH}_3$	2-Cl-phenyl	2-(methylsulfonyl)phenyl
375	$\text{SOCH}_3$	2-Cl-phenyl	4-morpholino
376	$\text{SOCH}_3$	2-Cl-phenyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
377	$\text{SOCH}_3$	2-Cl-phenyl	4-morpholinocarbonyl
378	$\text{SOCH}_3$	2-Cl-phenyl	2-methyl-1-imidazolyl
379	$\text{SOCH}_3$	2-Cl-phenyl	5-methyl-1-imidazolyl
380	$\text{SOCH}_3$	2-Cl-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
381	$\text{SOCH}_3$	2-F-phenyl	2-(aminosulfonyl)phenyl
382	$\text{SOCH}_3$	2-F-phenyl	2-(methylaminosulfonyl)phenyl
383	$\text{SOCH}_3$	2-F-phenyl	1-pyrrolidinocarbonyl
384	$\text{SOCH}_3$	2-F-phenyl	2-(methylsulfonyl)phenyl
385	$\text{SOCH}_3$	2-F-phenyl	4-morpholino
386	$\text{SOCH}_3$	2-F-phenyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
387	$\text{SOCH}_3$	2-F-phenyl	4-morpholinocarbonyl

388	$\text{SOCH}_3$	2-F-phenyl	2-methyl-1-imidazolyl
389	$\text{SOCH}_3$	2-F-phenyl	5-methyl-1-imidazolyl
390	$\text{SOCH}_3$	2-F-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
391	$\text{SOCH}_3$	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
392	$\text{SOCH}_3$	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
393	$\text{SOCH}_3$	2,6-diF-phenyl	1-pyrrolidinocarbonyl
394	$\text{SOCH}_3$	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
395	$\text{SOCH}_3$	2,6-diF-phenyl	4-morpholino
396	$\text{SOCH}_3$	2,6-diF-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
397	$\text{SOCH}_3$	2,6-diF-phenyl	4-morpholinocarbonyl
398	$\text{SOCH}_3$	2,6-diF-phenyl	2-methyl-1-imidazolyl
399	$\text{SOCH}_3$	2,6-diF-phenyl	5-methyl-1-imidazolyl
400	$\text{SOCH}_3$	2,6-diF-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
401	$\text{SO}_2\text{CH}_3$	phenyl	2-(aminosulfonyl)phenyl
402	$\text{SO}_2\text{CH}_3$	phenyl	2-(methylaminosulfonyl)phenyl
403	$\text{SO}_2\text{CH}_3$	phenyl	1-pyrrolidinocarbonyl
404	$\text{SO}_2\text{CH}_3$	phenyl	2-(methylsulfonyl)phenyl
405	$\text{SO}_2\text{CH}_3$	phenyl	4-morpholino
406	$\text{SO}_2\text{CH}_3$	phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
407	$\text{SO}_2\text{CH}_3$	phenyl	4-morpholinocarbonyl
408	$\text{SO}_2\text{CH}_3$	phenyl	2-methyl-1-imidazolyl
409	$\text{SO}_2\text{CH}_3$	phenyl	5-methyl-1-imidazolyl
410	$\text{SO}_2\text{CH}_3$	phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
411	$\text{SO}_2\text{CH}_3$	2-pyridyl	2-(aminosulfonyl)phenyl
412	$\text{SO}_2\text{CH}_3$	2-pyridyl	2-(methylaminosulfonyl)phenyl
413	$\text{SO}_2\text{CH}_3$	2-pyridyl	1-pyrrolidinocarbonyl
414	$\text{SO}_2\text{CH}_3$	2-pyridyl	2-(methylsulfonyl)phenyl
415	$\text{SO}_2\text{CH}_3$	2-pyridyl	4-morpholino
416	$\text{SO}_2\text{CH}_3$	2-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
417	$\text{SO}_2\text{CH}_3$	2-pyridyl	4-morpholinocarbonyl
418	$\text{SO}_2\text{CH}_3$	2-pyridyl	2-methyl-1-imidazolyl
419	$\text{SO}_2\text{CH}_3$	2-pyridyl	5-methyl-1-imidazolyl
420	$\text{SO}_2\text{CH}_3$	2-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
421	$\text{SO}_2\text{CH}_3$	3-pyridyl	2-(aminosulfonyl)phenyl
422	$\text{SO}_2\text{CH}_3$	3-pyridyl	2-(methylaminosulfonyl)phenyl
423	$\text{SO}_2\text{CH}_3$	3-pyridyl	1-pyrrolidinocarbonyl
424	$\text{SO}_2\text{CH}_3$	3-pyridyl	2-(methylsulfonyl)phenyl

425	$\text{SO}_2\text{CH}_3$	3-pyridyl	4-morpholino
426	$\text{SO}_2\text{CH}_3$	3-pyridyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
427	$\text{SO}_2\text{CH}_3$	3-pyridyl	4-morpholinocarbonyl
428	$\text{SO}_2\text{CH}_3$	3-pyridyl	2-methyl-1-imidazolyl
429	$\text{SO}_2\text{CH}_3$	3-pyridyl	5-methyl-1-imidazolyl
430	$\text{SO}_2\text{CH}_3$	3-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
431	$\text{SO}_2\text{CH}_3$	2-pyrimidyl	2-(aminosulfonyl)phenyl
432	$\text{SO}_2\text{CH}_3$	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
433	$\text{SO}_2\text{CH}_3$	2-pyrimidyl	1-pyrrolidinocarbonyl
434	$\text{SO}_2\text{CH}_3$	2-pyrimidyl	2-(methylsulfonyl)phenyl
435	$\text{SO}_2\text{CH}_3$	2-pyrimidyl	4-morpholino
436	$\text{SO}_2\text{CH}_3$	2-pyrimidyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
437	$\text{SO}_2\text{CH}_3$	2-pyrimidyl	4-morpholinocarbonyl
438	$\text{SO}_2\text{CH}_3$	2-pyrimidyl	2-methyl-1-imidazolyl
439	$\text{SO}_2\text{CH}_3$	2-pyrimidyl	5-methyl-1-imidazolyl
440	$\text{SO}_2\text{CH}_3$	2-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
441	$\text{SO}_2\text{CH}_3$	5-pyrimidyl	2-(aminosulfonyl)phenyl
442	$\text{SO}_2\text{CH}_3$	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
443	$\text{SO}_2\text{CH}_3$	5-pyrimidyl	1-pyrrolidinocarbonyl
444	$\text{SO}_2\text{CH}_3$	5-pyrimidyl	2-(methylsulfonyl)phenyl
445	$\text{SO}_2\text{CH}_3$	5-pyrimidyl	4-morpholino
446	$\text{SO}_2\text{CH}_3$	5-pyrimidyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
447	$\text{SO}_2\text{CH}_3$	5-pyrimidyl	4-morpholinocarbonyl
448	$\text{SO}_2\text{CH}_3$	5-pyrimidyl	2-methyl-1-imidazolyl
449	$\text{SO}_2\text{CH}_3$	5-pyrimidyl	5-methyl-1-imidazolyl
450	$\text{SO}_2\text{CH}_3$	5-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
451	$\text{SO}_2\text{CH}_3$	2-Cl-phenyl	2-(aminosulfonyl)phenyl
452	$\text{SO}_2\text{CH}_3$	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
453	$\text{SO}_2\text{CH}_3$	2-Cl-phenyl	1-pyrrolidinocarbonyl
454	$\text{SO}_2\text{CH}_3$	2-Cl-phenyl	2-(methylsulfonyl)phenyl
455	$\text{SO}_2\text{CH}_3$	2-Cl-phenyl	4-morpholino
456	$\text{SO}_2\text{CH}_3$	2-Cl-phenyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
457	$\text{SO}_2\text{CH}_3$	2-Cl-phenyl	4-morpholinocarbonyl
458	$\text{SO}_2\text{CH}_3$	2-Cl-phenyl	2-methyl-1-imidazolyl
459	$\text{SO}_2\text{CH}_3$	2-Cl-phenyl	5-methyl-1-imidazolyl
460	$\text{SO}_2\text{CH}_3$	2-Cl-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
461	$\text{SO}_2\text{CH}_3$	2-F-phenyl	2-(aminosulfonyl)phenyl

462	$\text{SO}_2\text{CH}_3$	2-F-phenyl	2-(methylaminosulfonyl)phenyl
463	$\text{SO}_2\text{CH}_3$	2-F-phenyl	1-pyrrolidinocarbonyl
464	$\text{SO}_2\text{CH}_3$	2-F-phenyl	2-(methylsulfonyl)phenyl
465	$\text{SO}_2\text{CH}_3$	2-F-phenyl	4-morpholino
466	$\text{SO}_2\text{CH}_3$	2-F-phenyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
467	$\text{SO}_2\text{CH}_3$	2-F-phenyl	4-morpholinocarbonyl
468	$\text{SO}_2\text{CH}_3$	2-F-phenyl	2-methyl-1-imidazolyl
469	$\text{SO}_2\text{CH}_3$	2-F-phenyl	5-methyl-1-imidazolyl
470	$\text{SO}_2\text{CH}_3$	2-F-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
471	$\text{SO}_2\text{CH}_3$	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
472	$\text{SO}_2\text{CH}_3$	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
473	$\text{SO}_2\text{CH}_3$	2,6-diF-phenyl	1-pyrrolidinocarbonyl
474	$\text{SO}_2\text{CH}_3$	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
475	$\text{SO}_2\text{CH}_3$	2,6-diF-phenyl	4-morpholino
476	$\text{SO}_2\text{CH}_3$	2,6-diF-phenyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
477	$\text{SO}_2\text{CH}_3$	2,6-diF-phenyl	4-morpholinocarbonyl
478	$\text{SO}_2\text{CH}_3$	2,6-diF-phenyl	2-methyl-1-imidazolyl
479	$\text{SO}_2\text{CH}_3$	2,6-diF-phenyl	5-methyl-1-imidazolyl
480	$\text{SO}_2\text{CH}_3$	2,6-diF-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
481	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	phenyl	2-(aminosulfonyl)phenyl
482	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	phenyl	2-(methylaminosulfonyl)phenyl
483	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	phenyl	1-pyrrolidinocarbonyl
484	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	phenyl	2-(methylsulfonyl)phenyl
485	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	phenyl	4-morpholino
486	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	phenyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
487	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	phenyl	4-morpholinocarbonyl
488	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	phenyl	2-methyl-1-imidazolyl
489	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	phenyl	5-methyl-1-imidazolyl

490	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	phenyl	2-methylsulfonyl-1-imidazolyl
491	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyridyl	2-(aminosulfonyl)phenyl
492	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyridyl	2-(methylaminosulfonyl)phenyl
493	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyridyl	1-pyrrolidinocarbonyl
494	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyridyl	2-(methylsulfonyl)phenyl
495	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyridyl	4-morpholino
496	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
497	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyridyl	4-morpholinocarbonyl
498	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyridyl	2-methyl-1-imidazolyl
499	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyridyl	5-methyl-1-imidazolyl
500	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyridyl	2-methylsulfonyl-1-imidazolyl
501	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	3-pyridyl	2-(aminosulfonyl)phenyl
502	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	3-pyridyl	2-(methylaminosulfonyl)phenyl
503	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	3-pyridyl	1-pyrrolidinocarbonyl
504	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	3-pyridyl	2-(methylsulfonyl)phenyl
505	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	3-pyridyl	4-morpholino
506	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	3-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
507	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	3-pyridyl	4-morpholinocarbonyl

508	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	3-pyridyl	2-methyl-1-imidazolyl
509	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	3-pyridyl	5-methyl-1-imidazolyl
510	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	3-pyridyl	2-methylsulfonyl-1-imidazolyl
511	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyrimidyl	2-(aminosulfonyl)phenyl
512	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
513	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyrimidyl	1-pyrrolidinocarbonyl
514	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyrimidyl	2-(methylsulfonyl)phenyl
515	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyrimidyl	4-morpholino
516	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyrimidyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
517	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyrimidyl	4-morpholinocarbonyl
518	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyrimidyl	2-methyl-1-imidazolyl
519	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyrimidyl	5-methyl-1-imidazolyl
520	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	2-pyrimidyl	2-methylsulfonyl-1-imidazolyl
521	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	5-pyrimidyl	2-(aminosulfonyl)phenyl
522	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
523	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	5-pyrimidyl	1-pyrrolidinocarbonyl
524	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	5-pyrimidyl	2-(methylsulfonyl)phenyl
525	$\text{CH}_2\text{NH}-\text{SO}_2\text{CH}_3$	5-pyrimidyl	4-morpholino

526	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	5-pyrimidyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
527	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	5-pyrimidyl	4-morpholinocarbonyl
528	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	5-pyrimidyl	2-methyl-1-imidazolyl
529	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	5-pyrimidyl	5-methyl-1-imidazolyl
530	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	5-pyrimidyl	2-methylsulfonyl-1-imidazolyl
531	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	2-Cl-phenyl	2-(aminosulfonyl)phenyl
532	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
533	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	2-Cl-phenyl	1-pyrrolidinocarbonyl
534	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	2-Cl-phenyl	2-(methylsulfonyl)phenyl
535	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	2-Cl-phenyl	4-morpholino
536	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	2-Cl-phenyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
537	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	2-Cl-phenyl	4-morpholinocarbonyl
538	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	2-Cl-phenyl	2-methyl-1-imidazolyl
539	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	2-Cl-phenyl	5-methyl-1-imidazolyl
540	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	2-Cl-phenyl	2-methylsulfonyl-1-imidazolyl
541	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	2-F-phenyl	2-(aminosulfonyl)phenyl
542	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	2-F-phenyl	2-(methylaminosulfonyl)phenyl
543	$\text{CH}_2\text{NH}-$ $\text{SO}_2\text{CH}_3$	2-F-phenyl	1-pyrrolidinocarbonyl

544	CH <sub>2</sub> NH-	2-F-phenyl	2-(methylsulfonyl)phenyl
	SO <sub>2</sub> CH <sub>3</sub>		
545	CH <sub>2</sub> NH-	2-F-phenyl	4-morpholino
	SO <sub>2</sub> CH <sub>3</sub>		
546	CH <sub>2</sub> NH-	2-F-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
	SO <sub>2</sub> CH <sub>3</sub>		
547	CH <sub>2</sub> NH-	2-F-phenyl	4-morpholinocarbonyl
	SO <sub>2</sub> CH <sub>3</sub>		
548	CH <sub>2</sub> NH-	2-F-phenyl	2-methyl-1-imidazolyl
	SO <sub>2</sub> CH <sub>3</sub>		
549	CH <sub>2</sub> NH-	2-F-phenyl	5-methyl-1-imidazolyl
	SO <sub>2</sub> CH <sub>3</sub>		
550	CH <sub>2</sub> NH-	2-F-phenyl	2-methylsulfonyl-1-imidazolyl
	SO <sub>2</sub> CH <sub>3</sub>		
551	CH <sub>2</sub> NH-	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
	SO <sub>2</sub> CH <sub>3</sub>		
552	CH <sub>2</sub> NH-	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
	SO <sub>2</sub> CH <sub>3</sub>		
553	CH <sub>2</sub> NH-	2,6-diF-phenyl	1-pyrrolidinocarbonyl
	SO <sub>2</sub> CH <sub>3</sub>		
554	CH <sub>2</sub> NH-	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
	SO <sub>2</sub> CH <sub>3</sub>		
555	CH <sub>2</sub> NH-	2,6-diF-phenyl	4-morpholino
	SO <sub>2</sub> CH <sub>3</sub>		
556	CH <sub>2</sub> NH-	2,6-diF-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
	SO <sub>2</sub> CH <sub>3</sub>		
557	CH <sub>2</sub> NH-	2,6-diF-phenyl	4-morpholinocarbonyl
	SO <sub>2</sub> CH <sub>3</sub>		
558	CH <sub>2</sub> NH-	2,6-diF-phenyl	2-methyl-1-imidazolyl
	SO <sub>2</sub> CH <sub>3</sub>		
559	CH <sub>2</sub> NH-	2,6-diF-phenyl	5-methyl-1-imidazolyl
	SO <sub>2</sub> CH <sub>3</sub>		
560	CH <sub>2</sub> NH-	2,6-diF-phenyl	2-methylsulfonyl-1-imidazolyl
	SO <sub>2</sub> CH <sub>3</sub>		
561	Cl	phenyl	2-(aminosulfonyl)phenyl
562	Cl	phenyl	2-(methylaminosulfonyl)phenyl
563	Cl	phenyl	1-pyrrolidinocarbonyl

564	C1	phenyl	2-(methylsulfonyl)phenyl
565	C1	phenyl	4-morpholino
566	C1	phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
567	C1	phenyl	4-morpholinocarbonyl
568	C1	phenyl	2-methyl-1-imidazolyl
569	C1	phenyl	5-methyl-1-imidazolyl
570	C1	phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
571	C1	2-pyridyl	2-(aminosulfonyl)phenyl
572	C1	2-pyridyl	2-(methylaminosulfonyl)phenyl
573	C1	2-pyridyl	1-pyrrolidinocarbonyl
574	C1	2-pyridyl	2-(methylsulfonyl)phenyl
575	C1	2-pyridyl	4-morpholino
576	C1	2-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
577	C1	2-pyridyl	4-morpholinocarbonyl
578	C1	2-pyridyl	2-methyl-1-imidazolyl
579	C1	2-pyridyl	5-methyl-1-imidazolyl
580	C1	2-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
581	C1	3-pyridyl	2-(aminosulfonyl)phenyl
582	C1	3-pyridyl	2-(methylaminosulfonyl)phenyl
583	C1	3-pyridyl	1-pyrrolidinocarbonyl
584	C1	3-pyridyl	2-(methylsulfonyl)phenyl
585	C1	3-pyridyl	4-morpholino
586	C1	3-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
587	C1	3-pyridyl	4-morpholinocarbonyl
588	C1	3-pyridyl	2-methyl-1-imidazolyl
589	C1	3-pyridyl	5-methyl-1-imidazolyl
590	C1	3-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
591	C1	2-pyrimidyl	2-(aminosulfonyl)phenyl
592	C1	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
593	C1	2-pyrimidyl	1-pyrrolidinocarbonyl
594	C1	2-pyrimidyl	2-(methylsulfonyl)phenyl
595	C1	2-pyrimidyl	4-morpholino
596	C1	2-pyrimidyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
597	C1	2-pyrimidyl	4-morpholinocarbonyl
598	C1	2-pyrimidyl	2-methyl-1-imidazolyl
599	C1	2-pyrimidyl	5-methyl-1-imidazolyl
600	C1	2-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>

601	C1	5-pyrimidyl	2-(aminosulfonyl)phenyl
602	C1	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
603	C1	5-pyrimidyl	1-pyrrolidinocarbonyl
604	C1	5-pyrimidyl	2-(methylsulfonyl)phenyl
605	C1	5-pyrimidyl	4-morpholino
606	C1	5-pyrimidyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
607	C1	5-pyrimidyl	4-morpholinocarbonyl
608	C1	5-pyrimidyl	2-methyl-1-imidazolyl
609	C1	5-pyrimidyl	5-methyl-1-imidazolyl
610	C1	5-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
611	C1	2-Cl-phenyl	2-(aminosulfonyl)phenyl
612	C1	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
613	C1	2-Cl-phenyl	1-pyrrolidinocarbonyl
614	C1	2-Cl-phenyl	2-(methylsulfonyl)phenyl
615	C1	2-Cl-phenyl	4-morpholino
616	C1	2-Cl-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
617	C1	2-Cl-phenyl	4-morpholinocarbonyl
618	C1	2-Cl-phenyl	2-methyl-1-imidazolyl
619	C1	2-Cl-phenyl	5-methyl-1-imidazolyl
620	C1	2-Cl-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
621	C1	2-F-phenyl	2-(aminosulfonyl)phenyl
622	C1	2-F-phenyl	2-(methylaminosulfonyl)phenyl
623	C1	2-F-phenyl	1-pyrrolidinocarbonyl
624	C1	2-F-phenyl	2-(methylsulfonyl)phenyl
625	C1	2-F-phenyl	4-morpholino
626	C1	2-F-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
627	C1	2-F-phenyl	4-morpholinocarbonyl
628	C1	2-F-phenyl	2-methyl-1-imidazolyl
629	C1	2-F-phenyl	5-methyl-1-imidazolyl
630	C1	2-F-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
631	C1	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
632	C1	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
633	C1	2,6-diF-phenyl	1-pyrrolidinocarbonyl
634	C1	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
635	C1	2,6-diF-phenyl	4-morpholino
636	C1	2,6-diF-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
637	C1	2,6-diF-phenyl	4-morpholinocarbonyl

638	C1	2,6-diF-phenyl	2-methyl-1-imidazolyl
639	C1	2,6-diF-phenyl	5-methyl-1-imidazolyl
640	C1	2,6-diF-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
641	F	phenyl	2-(aminosulfonyl)phenyl
642	F	phenyl	2-(methylaminosulfonyl)phenyl
643	F	phenyl	1-pyrrolidinocarbonyl
644	F	phenyl	2-(methylsulfonyl)phenyl
645	F	phenyl	4-morpholino
646	F	phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
647	F	phenyl	4-morpholinocarbonyl
648	F	phenyl	2-methyl-1-imidazolyl
649	F	phenyl	5-methyl-1-imidazolyl
650	F	phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
651	F	2-pyridyl	2-(aminosulfonyl)phenyl
652	F	2-pyridyl	2-(methylaminosulfonyl)phenyl
653	F	2-pyridyl	1-pyrrolidinocarbonyl
654	F	2-pyridyl	2-(methylsulfonyl)phenyl
655	F	2-pyridyl	4-morpholino
656	F	2-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
657	F	2-pyridyl	4-morpholinocarbonyl
658	F	2-pyridyl	2-methyl-1-imidazolyl
659	F	2-pyridyl	5-methyl-1-imidazolyl
660	F	2-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
661	F	3-pyridyl	2-(aminosulfonyl)phenyl
662	F	3-pyridyl	2-(methylaminosulfonyl)phenyl
663	F	3-pyridyl	1-pyrrolidinocarbonyl
664	F	3-pyridyl	2-(methylsulfonyl)phenyl
665	F	3-pyridyl	4-morpholino
666	F	3-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
667	F	3-pyridyl	4-morpholinocarbonyl
668	F	3-pyridyl	2-methyl-1-imidazolyl
669	F	3-pyridyl	5-methyl-1-imidazolyl
670	F	3-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
671	F	2-pyrimidyl	2-(aminosulfonyl)phenyl
672	F	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
673	F	2-pyrimidyl	1-pyrrolidinocarbonyl
674	F	2-pyrimidyl	2-(methylsulfonyl)phenyl

675	F	2-pyrimidyl	4-morpholino
676	F	2-pyrimidyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
677	F	2-pyrimidyl	4-morpholinocarbonyl
678	F	2-pyrimidyl	2-methyl-1-imidazolyl
679	F	2-pyrimidyl	5-methyl-1-imidazolyl
680	F	2-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
681	F	5-pyrimidyl	2-(aminosulfonyl)phenyl
682	F	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
683	F	5-pyrimidyl	1-pyrrolidinocarbonyl
684	F	5-pyrimidyl	2-(methylsulfonyl)phenyl
685	F	5-pyrimidyl	4-morpholino
686	F	5-pyrimidyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
687	F	5-pyrimidyl	4-morpholinocarbonyl
688	F	5-pyrimidyl	2-methyl-1-imidazolyl
689	F	5-pyrimidyl	5-methyl-1-imidazolyl
690	F	5-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
691	F	2-Cl-phenyl	2-(aminosulfonyl)phenyl
692	F	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
693	F	2-Cl-phenyl	1-pyrrolidinocarbonyl
694	F	2-Cl-phenyl	2-(methylsulfonyl)phenyl
695	F	2-Cl-phenyl	4-morpholino
696	F	2-Cl-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
697	F	2-Cl-phenyl	4-morpholinocarbonyl
698	F	2-Cl-phenyl	2-methyl-1-imidazolyl
699	F	2-Cl-phenyl	5-methyl-1-imidazolyl
700	F	2-Cl-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
701	F	2-F-phenyl	2-(aminosulfonyl)phenyl
702	F	2-F-phenyl	2-(methylaminosulfonyl)phenyl
703	F	2-F-phenyl	1-pyrrolidinocarbonyl
704	F	2-F-phenyl	2-(methylsulfonyl)phenyl
705	F	2-F-phenyl	4-morpholino
706	F	2-F-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
707	F	2-F-phenyl	4-morpholinocarbonyl
708	F	2-F-phenyl	2-methyl-1-imidazolyl
709	F	2-F-phenyl	5-methyl-1-imidazolyl
710	F	2-F-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
711	F	2,6-diF-phenyl	2-(aminosulfonyl)phenyl

712	F	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
713	F	2,6-diF-phenyl	1-pyrrolidinocarbonyl
714	F	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
715	F	2,6-diF-phenyl	4-morpholino
716	F	2,6-diF-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
717	F	2,6-diF-phenyl	4-morpholinocarbonyl
718	F	2,6-diF-phenyl	2-methyl-1-imidazolyl
719	F	2,6-diF-phenyl	5-methyl-1-imidazolyl
720	F	2,6-diF-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
721	CO <sub>2</sub> CH <sub>3</sub>	phenyl	2-(aminosulfonyl)phenyl
722	CO <sub>2</sub> CH <sub>3</sub>	phenyl	2-(methylaminosulfonyl)phenyl
723	CO <sub>2</sub> CH <sub>3</sub>	phenyl	1-pyrrolidinocarbonyl
724	CO <sub>2</sub> CH <sub>3</sub>	phenyl	2-(methylsulfonyl)phenyl
725	CO <sub>2</sub> CH <sub>3</sub>	phenyl	4-morpholino
726	CO <sub>2</sub> CH <sub>3</sub>	phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
727	CO <sub>2</sub> CH <sub>3</sub>	phenyl	4-morpholinocarbonyl
728	CO <sub>2</sub> CH <sub>3</sub>	phenyl	2-methyl-1-imidazolyl
729	CO <sub>2</sub> CH <sub>3</sub>	phenyl	5-methyl-1-imidazolyl
730	CO <sub>2</sub> CH <sub>3</sub>	phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
731	CO <sub>2</sub> CH <sub>3</sub>	2-pyridyl	2-(aminosulfonyl)phenyl
732	CO <sub>2</sub> CH <sub>3</sub>	2-pyridyl	2-(methylaminosulfonyl)phenyl
733	CO <sub>2</sub> CH <sub>3</sub>	2-pyridyl	1-pyrrolidinocarbonyl
734	CO <sub>2</sub> CH <sub>3</sub>	2-pyridyl	2-(methylsulfonyl)phenyl
735	CO <sub>2</sub> CH <sub>3</sub>	2-pyridyl	4-morpholino
736	CO <sub>2</sub> CH <sub>3</sub>	2-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
737	CO <sub>2</sub> CH <sub>3</sub>	2-pyridyl	4-morpholinocarbonyl
738	CO <sub>2</sub> CH <sub>3</sub>	2-pyridyl	2-methyl-1-imidazolyl
739	CO <sub>2</sub> CH <sub>3</sub>	2-pyridyl	5-methyl-1-imidazolyl
740	CO <sub>2</sub> CH <sub>3</sub>	2-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
741	CO <sub>2</sub> CH <sub>3</sub>	3-pyridyl	2-(aminosulfonyl)phenyl
742	CO <sub>2</sub> CH <sub>3</sub>	3-pyridyl	2-(methylaminosulfonyl)phenyl
743	CO <sub>2</sub> CH <sub>3</sub>	3-pyridyl	1-pyrrolidinocarbonyl
744	CO <sub>2</sub> CH <sub>3</sub>	3-pyridyl	2-(methylsulfonyl)phenyl
745	CO <sub>2</sub> CH <sub>3</sub>	3-pyridyl	4-morpholino
746	CO <sub>2</sub> CH <sub>3</sub>	3-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
747	CO <sub>2</sub> CH <sub>3</sub>	3-pyridyl	4-morpholinocarbonyl
748	CO <sub>2</sub> CH <sub>3</sub>	3-pyridyl	2-methyl-1-imidazolyl

749	$\text{CO}_2\text{CH}_3$	3-pyridyl	5-methyl-1-imidazolyl
750	$\text{CO}_2\text{CH}_3$	3-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
751	$\text{CO}_2\text{CH}_3$	2-pyrimidyl	2-(aminosulfonyl)phenyl
752	$\text{CO}_2\text{CH}_3$	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
753	$\text{CO}_2\text{CH}_3$	2-pyrimidyl	1-pyrrolidinocarbonyl
754	$\text{CO}_2\text{CH}_3$	2-pyrimidyl	2-(methylsulfonyl)phenyl
755	$\text{CO}_2\text{CH}_3$	2-pyrimidyl	4-morpholino
756	$\text{CO}_2\text{CH}_3$	2-pyrimidyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
757	$\text{CO}_2\text{CH}_3$	2-pyrimidyl	4-morpholinocarbonyl
758	$\text{CO}_2\text{CH}_3$	2-pyrimidyl	2-methyl-1-imidazolyl
759	$\text{CO}_2\text{CH}_3$	2-pyrimidyl	5-methyl-1-imidazolyl
760	$\text{CO}_2\text{CH}_3$	2-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
761	$\text{CO}_2\text{CH}_3$	5-pyrimidyl	2-(aminosulfonyl)phenyl
762	$\text{CO}_2\text{CH}_3$	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
763	$\text{CO}_2\text{CH}_3$	5-pyrimidyl	1-pyrrolidinocarbonyl
764	$\text{CO}_2\text{CH}_3$	5-pyrimidyl	2-(methylsulfonyl)phenyl
765	$\text{CO}_2\text{CH}_3$	5-pyrimidyl	4-morpholino
766	$\text{CO}_2\text{CH}_3$	5-pyrimidyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
767	$\text{CO}_2\text{CH}_3$	5-pyrimidyl	4-morpholinocarbonyl
768	$\text{CO}_2\text{CH}_3$	5-pyrimidyl	2-methyl-1-imidazolyl
769	$\text{CO}_2\text{CH}_3$	5-pyrimidyl	5-methyl-1-imidazolyl
770	$\text{CO}_2\text{CH}_3$	5-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
771	$\text{CO}_2\text{CH}_3$	2-Cl-phenyl	2-(aminosulfonyl)phenyl
772	$\text{CO}_2\text{CH}_3$	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
773	$\text{CO}_2\text{CH}_3$	2-Cl-phenyl	1-pyrrolidinocarbonyl
774	$\text{CO}_2\text{CH}_3$	2-Cl-phenyl	2-(methylsulfonyl)phenyl
775	$\text{CO}_2\text{CH}_3$	2-Cl-phenyl	4-morpholino
776	$\text{CO}_2\text{CH}_3$	2-Cl-phenyl	2-(1'- $\text{CF}_3$ -tetrazol-2-yl)phenyl
777	$\text{CO}_2\text{CH}_3$	2-Cl-phenyl	4-morpholinocarbonyl
778	$\text{CO}_2\text{CH}_3$	2-Cl-phenyl	2-methyl-1-imidazolyl
779	$\text{CO}_2\text{CH}_3$	2-Cl-phenyl	5-methyl-1-imidazolyl
780	$\text{CO}_2\text{CH}_3$	2-Cl-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
781	$\text{CO}_2\text{CH}_3$	2-F-phenyl	2-(aminosulfonyl)phenyl
782	$\text{CO}_2\text{CH}_3$	2-F-phenyl	2-(methylaminosulfonyl)phenyl
783	$\text{CO}_2\text{CH}_3$	2-F-phenyl	1-pyrrolidinocarbonyl
784	$\text{CO}_2\text{CH}_3$	2-F-phenyl	2-(methylsulfonyl)phenyl
785	$\text{CO}_2\text{CH}_3$	2-F-phenyl	4-morpholino

786	CO <sub>2</sub> CH <sub>3</sub>	2-F-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
787	CO <sub>2</sub> CH <sub>3</sub>	2-F-phenyl	4-morpholinocarbonyl
788	CO <sub>2</sub> CH <sub>3</sub>	2-F-phenyl	2-methyl-1-imidazolyl
789	CO <sub>2</sub> CH <sub>3</sub>	2-F-phenyl	5-methyl-1-imidazolyl
790	CO <sub>2</sub> CH <sub>3</sub>	2-F-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
791	CO <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
792	CO <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
793	CO <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	1-pyrrolidinocarbonyl
794	CO <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
795	CO <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	4-morpholino
796	CO <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
797	CO <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	4-morpholinocarbonyl
798	CO <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	2-methyl-1-imidazolyl
799	CO <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	5-methyl-1-imidazolyl
800	CO <sub>2</sub> CH <sub>3</sub>	2,6-diF-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
801	CH <sub>2</sub> OCH <sub>3</sub>	phenyl	2-(aminosulfonyl)phenyl
802	CH <sub>2</sub> OCH <sub>3</sub>	phenyl	2-(methylaminosulfonyl)phenyl
803	CH <sub>2</sub> OCH <sub>3</sub>	phenyl	1-pyrrolidinocarbonyl
804	CH <sub>2</sub> OCH <sub>3</sub>	phenyl	2-(methylsulfonyl)phenyl
805	CH <sub>2</sub> OCH <sub>3</sub>	phenyl	4-morpholino
806	CH <sub>2</sub> OCH <sub>3</sub>	phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
807	CH <sub>2</sub> OCH <sub>3</sub>	phenyl	4-morpholinocarbonyl
808	CH <sub>2</sub> OCH <sub>3</sub>	phenyl	2-methyl-1-imidazolyl
809	CH <sub>2</sub> OCH <sub>3</sub>	phenyl	5-methyl-1-imidazolyl
810	CH <sub>2</sub> OCH <sub>3</sub>	phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
811	CH <sub>2</sub> OCH <sub>3</sub>	2-pyridyl	2-(aminosulfonyl)phenyl
812	CH <sub>2</sub> OCH <sub>3</sub>	2-pyridyl	2-(methylaminosulfonyl)phenyl
813	CH <sub>2</sub> OCH <sub>3</sub>	2-pyridyl	1-pyrrolidinocarbonyl
814	CH <sub>2</sub> OCH <sub>3</sub>	2-pyridyl	2-(methylsulfonyl)phenyl
815	CH <sub>2</sub> OCH <sub>3</sub>	2-pyridyl	4-morpholino
816	CH <sub>2</sub> OCH <sub>3</sub>	2-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
817	CH <sub>2</sub> OCH <sub>3</sub>	2-pyridyl	4-morpholinocarbonyl
818	CH <sub>2</sub> OCH <sub>3</sub>	2-pyridyl	2-methyl-1-imidazolyl
819	CH <sub>2</sub> OCH <sub>3</sub>	2-pyridyl	5-methyl-1-imidazolyl
820	CH <sub>2</sub> OCH <sub>3</sub>	2-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
821	CH <sub>2</sub> OCH <sub>3</sub>	3-pyridyl	2-(aminosulfonyl)phenyl
822	CH <sub>2</sub> OCH <sub>3</sub>	3-pyridyl	2-(methylaminosulfonyl)phenyl

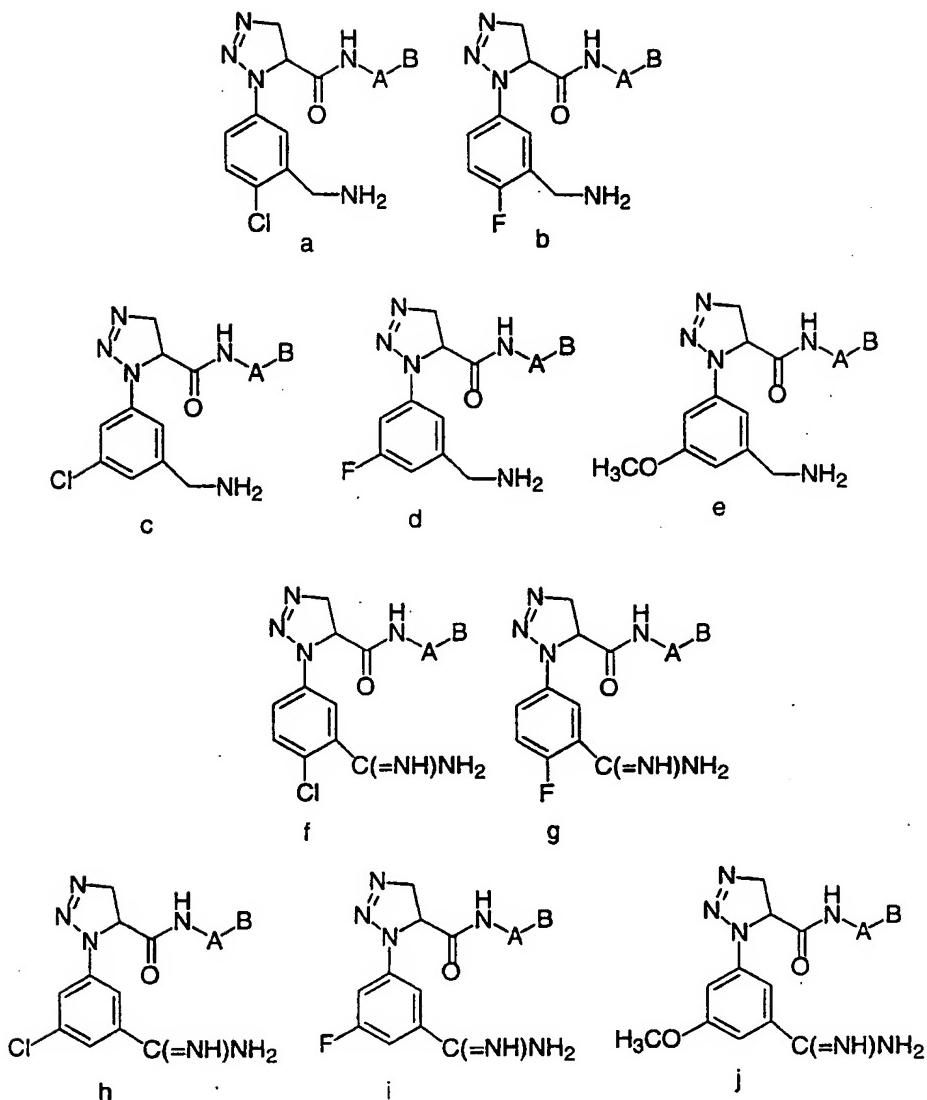
823	CH <sub>2</sub> OCH <sub>3</sub>	3-pyridyl	1-pyrrolidinocarbonyl
824	CH <sub>2</sub> OCH <sub>3</sub>	3-pyridyl	2-(methylsulfonyl)phenyl
825	CH <sub>2</sub> OCH <sub>3</sub>	3-pyridyl	4-morpholino
826	CH <sub>2</sub> OCH <sub>3</sub>	3-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
827	CH <sub>2</sub> OCH <sub>3</sub>	3-pyridyl	4-morpholinocarbonyl
828	CH <sub>2</sub> OCH <sub>3</sub>	3-pyridyl	2-methyl-1-imidazolyl
829	CH <sub>2</sub> OCH <sub>3</sub>	3-pyridyl	5-methyl-1-imidazolyl
830	CH <sub>2</sub> OCH <sub>3</sub>	3-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
831	CH <sub>2</sub> OCH <sub>3</sub>	2-pyrimidyl	2-(aminosulfonyl)phenyl
832	CH <sub>2</sub> OCH <sub>3</sub>	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
833	CH <sub>2</sub> OCH <sub>3</sub>	2-pyrimidyl	1-pyrrolidinocarbonyl
834	CH <sub>2</sub> OCH <sub>3</sub>	2-pyrimidyl	2-(methylsulfonyl)phenyl
835	CH <sub>2</sub> OCH <sub>3</sub>	2-pyrimidyl	4-morpholino
836	CH <sub>2</sub> OCH <sub>3</sub>	2-pyrimidyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
837	CH <sub>2</sub> OCH <sub>3</sub>	2-pyrimidyl	4-morpholinocarbonyl
838	CH <sub>2</sub> OCH <sub>3</sub>	2-pyrimidyl	2-methyl-1-imidazolyl
839	CH <sub>2</sub> OCH <sub>3</sub>	2-pyrimidyl	5-methyl-1-imidazolyl
840	CH <sub>2</sub> OCH <sub>3</sub>	2-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
841	CH <sub>2</sub> OCH <sub>3</sub>	5-pyrimidyl	2-(aminosulfonyl)phenyl
842	CH <sub>2</sub> OCH <sub>3</sub>	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
843	CH <sub>2</sub> OCH <sub>3</sub>	5-pyrimidyl	1-pyrrolidinocarbonyl
844	CH <sub>2</sub> OCH <sub>3</sub>	5-pyrimidyl	2-(methylsulfonyl)phenyl
845	CH <sub>2</sub> OCH <sub>3</sub>	5-pyrimidyl	4-morpholino
846	CH <sub>2</sub> OCH <sub>3</sub>	5-pyrimidyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
847	CH <sub>2</sub> OCH <sub>3</sub>	5-pyrimidyl	4-morpholinocarbonyl
848	CH <sub>2</sub> OCH <sub>3</sub>	5-pyrimidyl	2-methyl-1-imidazolyl
849	CH <sub>2</sub> OCH <sub>3</sub>	5-pyrimidyl	5-methyl-1-imidazolyl
850	CH <sub>2</sub> OCH <sub>3</sub>	5-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
851	CH <sub>2</sub> OCH <sub>3</sub>	2-Cl-phenyl	2-(aminosulfonyl)phenyl
852	CH <sub>2</sub> OCH <sub>3</sub>	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
853	CH <sub>2</sub> OCH <sub>3</sub>	2-Cl-phenyl	1-pyrrolidinocarbonyl
854	CH <sub>2</sub> OCH <sub>3</sub>	2-Cl-phenyl	2-(methylsulfonyl)phenyl
855	CH <sub>2</sub> OCH <sub>3</sub>	2-Cl-phenyl	4-morpholino
856	CH <sub>2</sub> OCH <sub>3</sub>	2-Cl-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
857	CH <sub>2</sub> OCH <sub>3</sub>	2-Cl-phenyl	4-morpholinocarbonyl
858	CH <sub>2</sub> OCH <sub>3</sub>	2-Cl-phenyl	2-methyl-1-imidazolyl
859	CH <sub>2</sub> OCH <sub>3</sub>	2-Cl-phenyl	5-methyl-1-imidazolyl

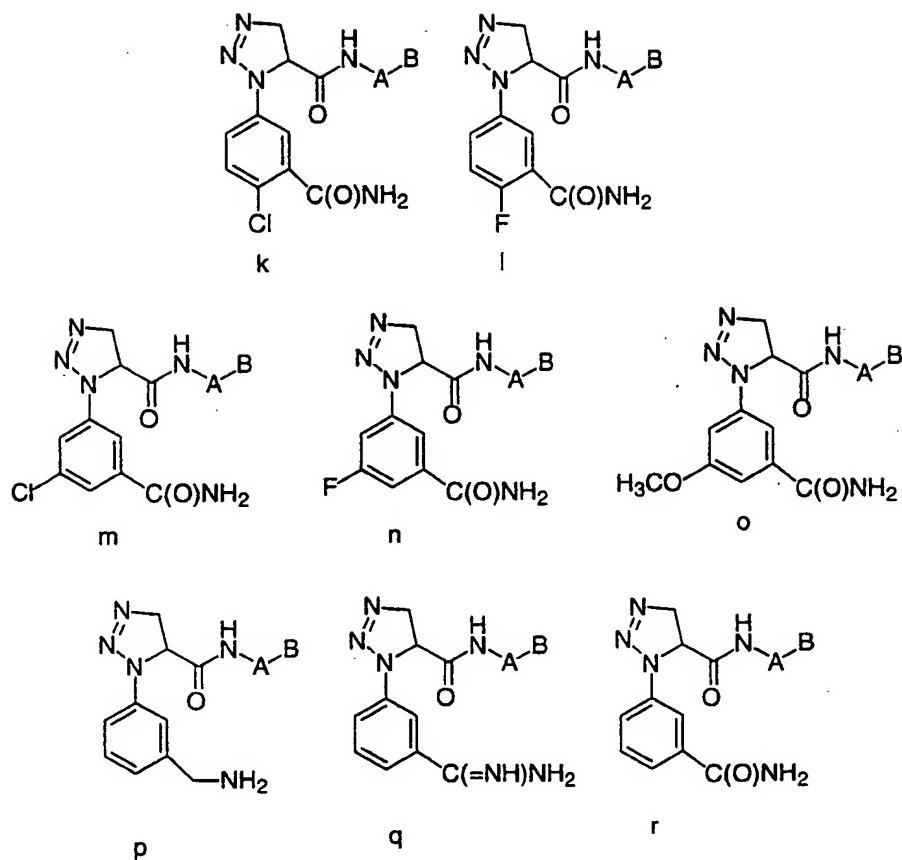
860	$\text{CH}_2\text{OCH}_3$	2-Cl-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
861	$\text{CH}_2\text{OCH}_3$	2-F-phenyl	2-(aminosulfonyl)phenyl
862	$\text{CH}_2\text{OCH}_3$	2-F-phenyl	2-(methylaminosulfonyl)phenyl
863	$\text{CH}_2\text{OCH}_3$	2-F-phenyl	1-pyrrolidinocarbonyl
864	$\text{CH}_2\text{OCH}_3$	2-F-phenyl	2-(methylsulfonyl)phenyl
865	$\text{CH}_2\text{OCH}_3$	2-F-phenyl	4-morpholino
866	$\text{CH}_2\text{OCH}_3$	2-F-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
867	$\text{CH}_2\text{OCH}_3$	2-F-phenyl	4-morpholinocarbonyl
868	$\text{CH}_2\text{OCH}_3$	2-F-phenyl	2-methyl-1-imidazolyl
869	$\text{CH}_2\text{OCH}_3$	2-F-phenyl	5-methyl-1-imidazolyl
870	$\text{CH}_2\text{OCH}_3$	2-F-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
871	$\text{CH}_2\text{OCH}_3$	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
872	$\text{CH}_2\text{OCH}_3$	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
873	$\text{CH}_2\text{OCH}_3$	2,6-diF-phenyl	1-pyrrolidinocarbonyl
874	$\text{CH}_2\text{OCH}_3$	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
875	$\text{CH}_2\text{OCH}_3$	2,6-diF-phenyl	4-morpholino
876	$\text{CH}_2\text{OCH}_3$	2,6-diF-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
877	$\text{CH}_2\text{OCH}_3$	2,6-diF-phenyl	4-morpholinocarbonyl
878	$\text{CH}_2\text{OCH}_3$	2,6-diF-phenyl	2-methyl-1-imidazolyl
879	$\text{CH}_2\text{OCH}_3$	2,6-diF-phenyl	5-methyl-1-imidazolyl
880	$\text{CH}_2\text{OCH}_3$	2,6-diF-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
881	$\text{CONH}_2$	phenyl	2-(aminosulfonyl)phenyl
882	$\text{CONH}_2$	phenyl	2-(methylaminosulfonyl)phenyl
883	$\text{CONH}_2$	phenyl	1-pyrrolidinocarbonyl
884	$\text{CONH}_2$	phenyl	2-(methylsulfonyl)phenyl
885	$\text{CONH}_2$	phenyl	4-morpholino
886	$\text{CONH}_2$	phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
887	$\text{CONH}_2$	phenyl	4-morpholinocarbonyl
888	$\text{CONH}_2$	phenyl	2-methyl-1-imidazolyl
889	$\text{CONH}_2$	phenyl	5-methyl-1-imidazolyl
890	$\text{CONH}_2$	phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
891	$\text{CONH}_2$	2-pyridyl	2-(aminosulfonyl)phenyl
892	$\text{CONH}_2$	2-pyridyl	2-(methylaminosulfonyl)phenyl
893	$\text{CONH}_2$	2-pyridyl	1-pyrrolidinocarbonyl
894	$\text{CONH}_2$	2-pyridyl	2-(methylsulfonyl)phenyl
895	$\text{CONH}_2$	2-pyridyl	4-morpholino
896	$\text{CONH}_2$	2-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl

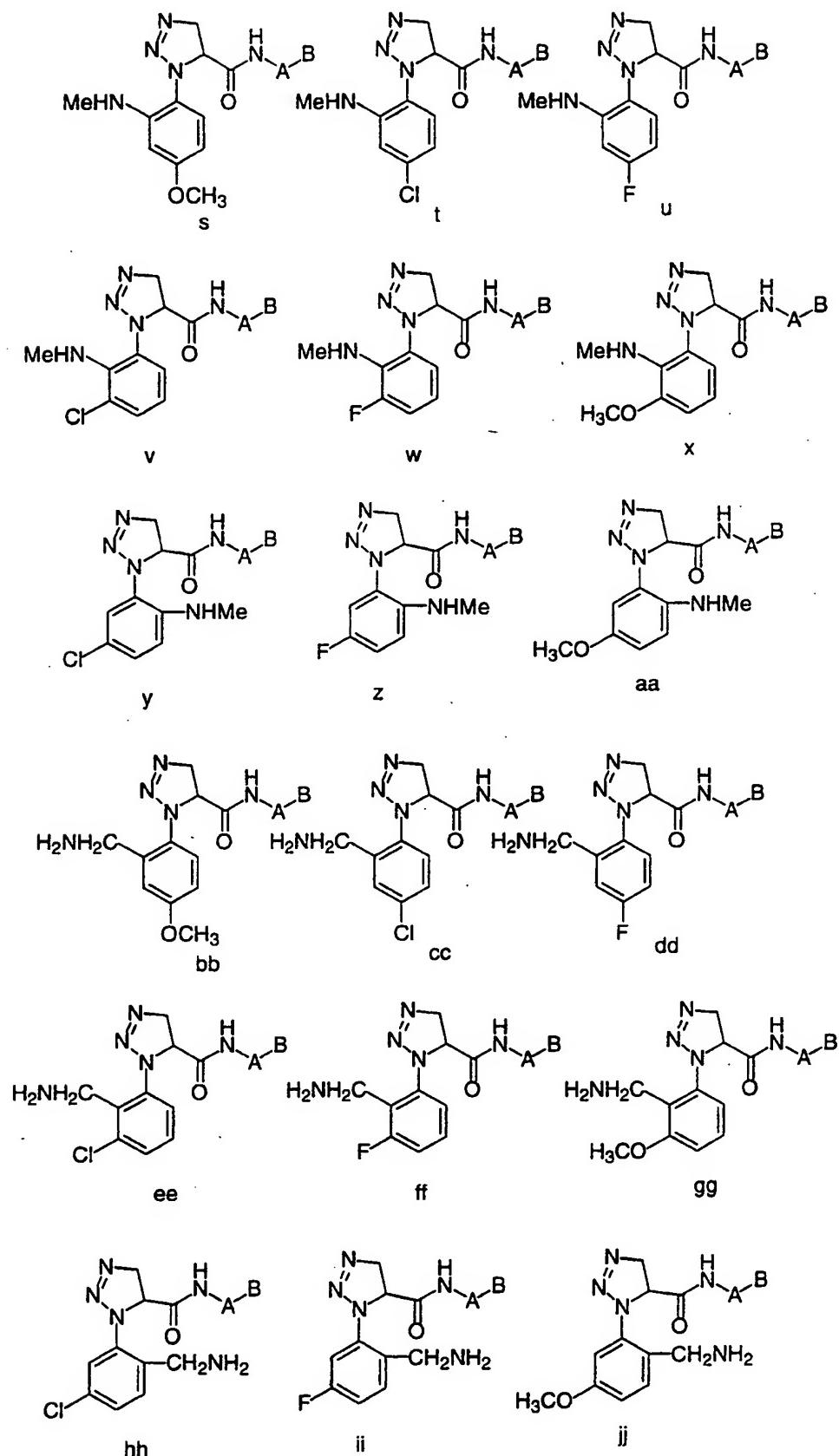
897	CONH <sub>2</sub>	2-pyridyl	4-morpholinocarbonyl
898	CONH <sub>2</sub>	2-pyridyl	2-methyl-1-imidazolyl
899	CONH <sub>2</sub>	2-pyridyl	5-methyl-1-imidazolyl
900	CONH <sub>2</sub>	2-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
901	CONH <sub>2</sub>	3-pyridyl	2-(aminosulfonyl)phenyl
902	CONH <sub>2</sub>	3-pyridyl	2-(methylaminosulfonyl)phenyl
903	CONH <sub>2</sub>	3-pyridyl	1-pyrrolidinocarbonyl
904	CONH <sub>2</sub>	3-pyridyl	2-(methylsulfonyl)phenyl
905	CONH <sub>2</sub>	3-pyridyl	4-morpholino
906	CONH <sub>2</sub>	3-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
907	CONH <sub>2</sub>	3-pyridyl	4-morpholinocarbonyl
908	CONH <sub>2</sub>	3-pyridyl	2-methyl-1-imidazolyl
909	CONH <sub>2</sub>	3-pyridyl	5-methyl-1-imidazolyl
910	CONH <sub>2</sub>	3-pyridyl	<u>2-methylsulfonyl-1-imidazolyl</u>
911	CONH <sub>2</sub>	2-pyrimidyl	2-(aminosulfonyl)phenyl
912	CONH <sub>2</sub>	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
913	CONH <sub>2</sub>	2-pyrimidyl	1-pyrrolidinocarbonyl
914	CONH <sub>2</sub>	2-pyrimidyl	2-(methylsulfonyl)phenyl
915	CONH <sub>2</sub>	2-pyrimidyl	4-morpholino
916	CONH <sub>2</sub>	2-pyrimidyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
917	CONH <sub>2</sub>	2-pyrimidyl	4-morpholinocarbonyl
918	CONH <sub>2</sub>	2-pyrimidyl	2-methyl-1-imidazolyl
919	CONH <sub>2</sub>	2-pyrimidyl	5-methyl-1-imidazolyl
920	CONH <sub>2</sub>	2-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
921	CONH <sub>2</sub>	5-pyrimidyl	2-(aminosulfonyl)phenyl
922	CONH <sub>2</sub>	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
923	CONH <sub>2</sub>	5-pyrimidyl	1-pyrrolidinocarbonyl
924	CONH <sub>2</sub>	5-pyrimidyl	2-(methylsulfonyl)phenyl
925	CONH <sub>2</sub>	5-pyrimidyl	4-morpholino
926	CONH <sub>2</sub>	5-pyrimidyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
927	CONH <sub>2</sub>	5-pyrimidyl	4-morpholinocarbonyl
928	CONH <sub>2</sub>	5-pyrimidyl	2-methyl-1-imidazolyl
929	CONH <sub>2</sub>	5-pyrimidyl	5-methyl-1-imidazolyl
930	CONH <sub>2</sub>	5-pyrimidyl	<u>2-methylsulfonyl-1-imidazolyl</u>
931	CONH <sub>2</sub>	2-Cl-phenyl	2-(aminosulfonyl)phenyl
932	CONH <sub>2</sub>	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
933	CONH <sub>2</sub>	2-Cl-phenyl	1-pyrrolidinocarbonyl

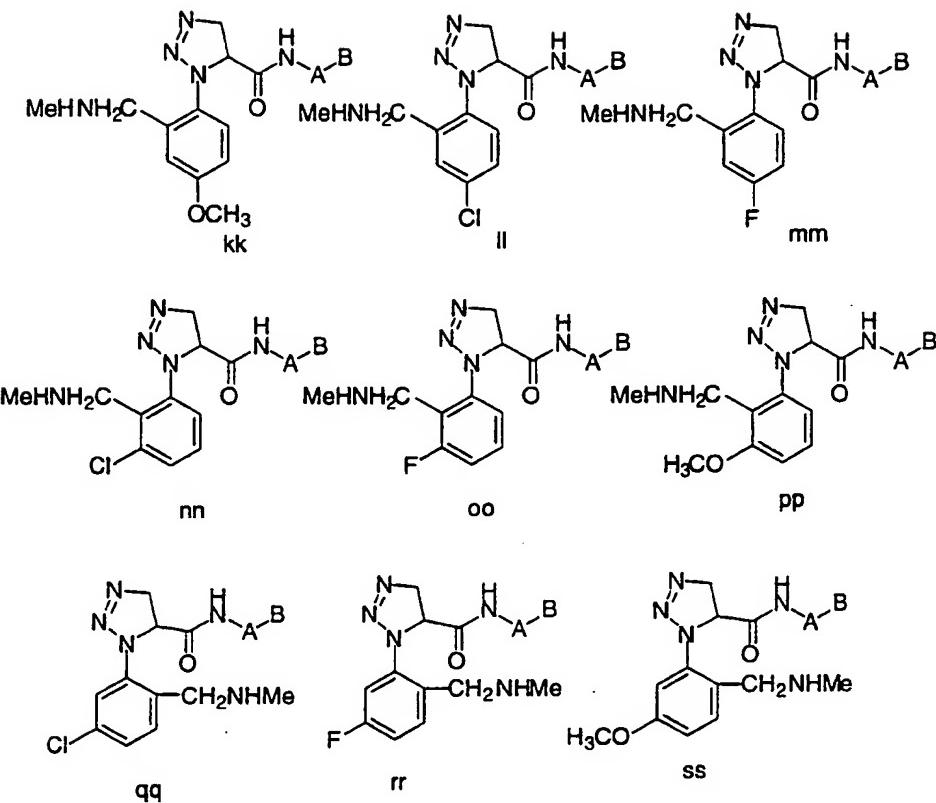
934	CONH <sub>2</sub>	2-Cl-phenyl	2-(methylsulfonyl)phenyl
935	CONH <sub>2</sub>	2-Cl-phenyl	4-morpholino
936	CONH <sub>2</sub>	2-Cl-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
937	CONH <sub>2</sub>	2-Cl-phenyl	4-morpholinocarbonyl
938	CONH <sub>2</sub>	2-Cl-phenyl	2-methyl-1-imidazolyl
939	CONH <sub>2</sub>	2-Cl-phenyl	5-methyl-1-imidazolyl
940	CONH <sub>2</sub>	2-Cl-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
941	CONH <sub>2</sub>	2-F-phenyl	2-(aminosulfonyl)phenyl
942	CONH <sub>2</sub>	2-F-phenyl	2-(methylaminosulfonyl)phenyl
943	CONH <sub>2</sub>	2-F-phenyl	1-pyrrolidinocarbonyl
944	CONH <sub>2</sub>	2-F-phenyl	2-(methylsulfonyl)phenyl
945	CONH <sub>2</sub>	2-F-phenyl	4-morpholino
946	CONH <sub>2</sub>	2-F-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
947	CONH <sub>2</sub>	2-F-phenyl	4-morpholinocarbonyl
948	CONH <sub>2</sub>	2-F-phenyl	2-methyl-1-imidazolyl
949	CONH <sub>2</sub>	2-F-phenyl	5-methyl-1-imidazolyl
950	CONH <sub>2</sub>	2-F-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
951	CONH <sub>2</sub>	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
952	CONH <sub>2</sub>	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
953	CONH <sub>2</sub>	2,6-diF-phenyl	1-pyrrolidinocarbonyl
954	CONH <sub>2</sub>	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
955	CONH <sub>2</sub>	2,6-diF-phenyl	4-morpholino
956	CONH <sub>2</sub>	2,6-diF-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
957	CONH <sub>2</sub>	2,6-diF-phenyl	4-morpholinocarbonyl
958	CONH <sub>2</sub>	2,6-diF-phenyl	2-methyl-1-imidazolyl
959	CONH <sub>2</sub>	2,6-diF-phenyl	5-methyl-1-imidazolyl
960	CONH <sub>2</sub>	2,6-diF-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>

Table 2









Ex #	A	B
1	phenyl	2-(aminosulfonyl)phenyl
2	phenyl	2-(methylaminosulfonyl)phenyl
3	phenyl	1-pyrrolidinocarbonyl
4	phenyl	2-(methylsulfonyl)phenyl
5	phenyl	4-morpholino
6	phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
7	phenyl	4-morpholinocarbonyl
8	phenyl	2-methyl-1-imidazolyl
9	phenyl	5-methyl-1-imidazolyl
10	phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
11	2-pyridyl	2-(aminosulfonyl)phenyl
12	2-pyridyl	2-(methylaminosulfonyl)phenyl
13	2-pyridyl	1-pyrrolidinocarbonyl
14	2-pyridyl	2-(methylsulfonyl)phenyl
15	2-pyridyl	4-morpholino
16	2-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
17	2-pyridyl	4-morpholinocarbonyl

18	2-pyridyl	2-methyl-1-imidazolyl
19	2-pyridyl	5-methyl-1-imidazolyl
20	<u>2-pyridyl</u>	<u>2-methylsulfonyl-1-imidazolyl</u>
21	3-pyridyl	2-(aminosulfonyl)phenyl
22	3-pyridyl	2-(methylaminosulfonyl)phenyl
23	3-pyridyl	1-pyrrolidinocarbonyl
24	3-pyridyl	2-(methylsulfonyl)phenyl
25	3-pyridyl	4-morpholino
26	3-pyridyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
27	3-pyridyl	4-morpholinocarbonyl
28	3-pyridyl	2-methyl-1-imidazolyl
29	3-pyridyl	5-methyl-1-imidazolyl
30	<u>3-pyridyl</u>	<u>2-methylsulfonyl-1-imidazolyl</u>
31	2-pyrimidyl	2-(aminosulfonyl)phenyl
32	2-pyrimidyl	2-(methylaminosulfonyl)phenyl
33	2-pyrimidyl	1-pyrrolidinocarbonyl
34	2-pyrimidyl	2-(methylsulfonyl)phenyl
35	2-pyrimidyl	4-morpholino
36	2-pyrimidyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
37	2-pyrimidyl	4-morpholinocarbonyl
38	2-pyrimidyl	2-methyl-1-imidazolyl
39	2-pyrimidyl	5-methyl-1-imidazolyl
40	<u>2-pyrimidyl</u>	<u>2-methylsulfonyl-1-imidazolyl</u>
41	5-pyrimidyl	2-(aminosulfonyl)phenyl
42	5-pyrimidyl	2-(methylaminosulfonyl)phenyl
43	5-pyrimidyl	1-pyrrolidinocarbonyl
44	5-pyrimidyl	2-(methylsulfonyl)phenyl
45	5-pyrimidyl	4-morpholino
46	5-pyrimidyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
47	5-pyrimidyl	4-morpholinocarbonyl
48	5-pyrimidyl	2-methyl-1-imidazolyl
49	5-pyrimidyl	5-methyl-1-imidazolyl
50	<u>5-pyrimidyl</u>	<u>2-methylsulfonyl-1-imidazolyl</u>
51	2-Cl-phenyl	2-(aminosulfonyl)phenyl
52	2-Cl-phenyl	2-(methylaminosulfonyl)phenyl
53	2-Cl-phenyl	1-pyrrolidinocarbonyl
54	2-Cl-phenyl	2-(methylsulfonyl)phenyl

55	2-Cl-phenyl	4-morpholino
56	2-Cl-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
57	2-Cl-phenyl	4-morpholinocarbonyl
58	2-Cl-phenyl	2-methyl-1-imidazolyl
59	2-Cl-phenyl	5-methyl-1-imidazolyl
60	2-Cl-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
61	2-F-phenyl	2-(aminosulfonyl)phenyl
62	2-F-phenyl	2-(methylaminosulfonyl)phenyl
63	2-F-phenyl	1-pyrrolidinocarbonyl
64	2-F-phenyl	2-(methylsulfonyl)phenyl
65	2-F-phenyl	4-morpholino
66	2-F-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
67	2-F-phenyl	4-morpholinocarbonyl
68	2-F-phenyl	2-methyl-1-imidazolyl
69	2-F-phenyl	5-methyl-1-imidazolyl
70	2-F-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>
71	2,6-diF-phenyl	2-(aminosulfonyl)phenyl
72	2,6-diF-phenyl	2-(methylaminosulfonyl)phenyl
73	2,6-diF-phenyl	1-pyrrolidinocarbonyl
74	2,6-diF-phenyl	2-(methylsulfonyl)phenyl
75	2,6-diF-phenyl	4-morpholino
76	2,6-diF-phenyl	2-(1'-CF <sub>3</sub> -tetrazol-2-yl)phenyl
77	2,6-diF-phenyl	4-morpholinocarbonyl
78	2,6-diF-phenyl	2-methyl-1-imidazolyl
79	2,6-diF-phenyl	5-methyl-1-imidazolyl
80	2,6-diF-phenyl	<u>2-methylsulfonyl-1-imidazolyl</u>

Utility

The compounds of this invention are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals. The term "thromboembolic disorders" as used herein includes arterial or venous cardiovascular or cerebrovascular thromboembolic disorders, including, for example, unstable angina, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack; stroke, atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism,

coronary and cerebral arterial thrombosis, cerebral embolism, kidney embolisms, and pulmonary embolisms. The anticoagulant effect of compounds of the present invention is believed to be due to inhibition of factor Xa or thrombin.

5       The effectiveness of compounds of the present invention as inhibitors of factor Xa was determined using purified human factor Xa and synthetic substrate. The rate of factor Xa hydrolysis of chromogenic substrate S2222 (Kabi Pharmacia, Franklin, OH) was measured both in the absence and presence of 10 compounds of the present invention. Hydrolysis of the substrate resulted in the release of pNA, which was monitored spectrophotometrically by measuring the increase in absorbance at 405 nm. A decrease in the rate of absorbance change at 405 nm in the presence of inhibitor is indicative of enzyme 15 inhibition. The results of this assay are expressed as inhibitory constant,  $K_i$ .

Factor Xa determinations were made in 0.10 M sodium phosphate buffer, pH 7.5, containing 0.20 M NaCl, and 0.5 % PEG 8000. The Michaelis constant,  $K_m$ , for substrate 20 hydrolysis was determined at 25°C using the method of Lineweaver and Burk. Values of  $K_i$  were determined by allowing 0.2-0.5 nM human factor Xa (Enzyme Research Laboratories, South Bend, IN) to react with the substrate (0.20 mM-1 mM) in the presence of inhibitor. Reactions were allowed to go for 25 30 minutes and the velocities (rate of absorbance change vs time) were measured in the time frame of 25-30 minutes. The following relationship was used to calculate  $K_i$  values:

$$(v_0 - v_s) / v_s = I / (K_i (1 + S/K_m))$$

where:

30        $v_0$  is the velocity of the control in the absence of inhibitor;  
 $v_s$  is the velocity in the presence of inhibitor;  
 $I$  is the concentration of inhibitor;  
 $K_i$  is the dissociation constant of the enzyme:inhibitor 35 complex;  
 $S$  is the concentration of substrate;  
 $K_m$  is the Michaelis constant.

Using the methodology described above, a compound of the present invention were found to exhibit a  $K_i$  of  $\leq 10 \mu\text{M}$ , thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors.

5       The antithrombotic effect of compounds of the present invention can be demonstrated in a rabbit arterio-venous (AV) shunt thrombosis model. In this model, rabbits weighing 2-3 kg anesthetized with a mixture of xylazine (10 mg/kg i.m.) and ketamine (50 mg/kg i.m.) are used. A saline-filled AV shunt  
10 device is connected between the femoral arterial and the femoral venous cannulae. The AV shunt device consists of a piece of 6-cm tygon tubing which contains a piece of silk thread. Blood will flow from the femoral artery via the AV-shunt into the femoral vein. The exposure of flowing blood to  
15 a silk thread will induce the formation of a significant thrombus. After forty minutes, the shunt is disconnected and the silk thread covered with thrombus is weighed. Test agents or vehicle will be given (i.v., i.p., s.c., or orally) prior to the opening of the AV shunt. The percentage inhibition of  
20 thrombus formation is determined for each treatment group. The ID<sub>50</sub> values (dose which produces 50% inhibition of thrombus formation) are estimated by linear regression.

The compounds of formula (I) may also be useful as  
inhibitors of serine proteases, notably human thrombin, plasma  
25 kallikrein and plasmin. Because of their inhibitory action, these compounds are indicated for use in the prevention or treatment of physiological reactions, blood coagulation and inflammation, catalyzed by the aforesaid class of enzymes. Specifically, the compounds have utility as drugs for the  
30 treatment of diseases arising from elevated thrombin activity such as myocardial infarction, and as reagents used as anticoagulants in the processing of blood to plasma for diagnostic and other commercial purposes.

Some compounds of the present invention were shown to be  
35 direct acting inhibitors of the serine protease thrombin by their ability to inhibit the cleavage of small molecule substrates by thrombin in a purified system. *In vitro* inhibition constants were determined by the method described

by Kettner et al. in *J. Biol. Chem.* **265**, 18289-18297 (1990), herein incorporated by reference. In these assays, thrombin-mediated hydrolysis of the chromogenic substrate S2238 (Helena Laboratories, Beaumont, TX) was monitored

5 spectrophotometrically. Addition of an inhibitor to the assay mixture results in decreased absorbance and is indicative of thrombin inhibition. Human thrombin (Enzyme Research Laboratories, Inc., South Bend, IN) at a concentration of 0.2 nM in 0.10 M sodium phosphate buffer, pH 7.5, 0.20 M NaCl, and  
10 0.5% PEG 6000, was incubated with various substrate concentrations ranging from 0.20 to 0.02 mM. After 25 to 30 minutes of incubation, thrombin activity was assayed by monitoring the rate of increase in absorbance at 405 nm which arises owing to substrate hydrolysis. Inhibition constants  
15 were derived from reciprocal plots of the reaction velocity as a function of substrate concentration using the standard method of Lineweaver and Burk. Using the methodology described above, some compounds of this invention were evaluated and found to exhibit a  $K_i$  of less than 10  $\mu\text{m}$ ,  
20 thereby confirming the utility of the compounds of the present invention as effective thrombin inhibitors.

The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. These include other anti-coagulant or coagulation inhibitory agents, anti-platelet or platelet inhibitory agents, thrombin inhibitors, or thrombolytic or fibrinolytic agents.

25 The compounds are administered to a mammal in a therapeutically effective amount. By "therapeutically effective amount" it is meant an amount of a compound of Formula I that, when administered alone or in combination with an additional therapeutic agent to a mammal, is effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

30 By "administered in combination" or "combination therapy" it is meant that the compound of Formula I and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination

each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect. Other anticoagulant agents (or coagulation inhibitory agents) that may be used in combination with the compounds of this invention include warfarin and heparin, as well as other factor Xa inhibitors such as those described in the publications identified above under Background of the Invention.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function such as by inhibiting the aggregation, adhesion or granular secretion of platelets. Such agents include, but are not limited to, the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfipyrazone, and piroxicam, including pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicylic acid or ASA), and piroxicam are preferred. Other suitable anti-platelet agents include ticlopidine, including pharmaceutically acceptable salts or prodrugs thereof. Ticlopidine is also a preferred compound since it is known to be gentle on the gastro-intestinal tract in use. Still other suitable platelet inhibitory agents include IIb/IIIa antagonists, thromboxane-A2-receptor antagonists and thromboxane-A2-synthetase inhibitors, as well as pharmaceutically acceptable salts or prodrugs thereof.

The term thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. A number of thrombin inhibitors are known to one of skill in the art and these inhibitors are contemplated to be used in combination with the present compounds. Such inhibitors include, but are

not limited to, boroarginine derivatives, boropeptides, heparins, hirudin and argatroban, including pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boropeptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal a-aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiouronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin. Boropeptide thrombin inhibitors include compounds described in Kettner et al., U.S. Patent No. 5,187,157 and European Patent Application Publication Number 293 881 A2, the disclosures of which are hereby incorporated herein by reference. Other suitable boroarginine derivatives and boropeptide thrombin inhibitors include those disclosed in PCT Application Publication Number 92/07869 and European Patent Application Publication Number 471,651 A2, the disclosures of which are hereby incorporated herein by reference.

The term thrombolytics (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator, anistreplase, urokinase or streptokinase, including pharmaceutically acceptable salts or prodrugs thereof. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in European Patent Application No. 028,489, the disclosure of which is hereby incorporated herein by reference herein. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

Administration of the compounds of Formula I of the invention in combination with such additional therapeutic agent, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety.

The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of factor Xa. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving factor Xa. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimenter that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

The compounds of the present invention may also be used in diagnostic assays involving factor Xa. For example, the presence of factor Xa in an unknown sample could be determined by addition of chromogenic substrate S2222 to a series of solutions containing test sample and optionally one of the compounds of the present invention. If production of pNA is observed in the solutions containing test sample, but not in the presence of a compound of the present invention, then one would conclude factor Xa was present.

25

#### Dosage and Formulation

The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, 5 age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian 10 can determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the thromboembolic disorder.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will 15 range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. 20 Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal 25 vehicles, or via transdermal routes, using transdermal skin patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

30 The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, 35 syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined

with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans,

polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Representative useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

5 A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

10 Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil may be prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules should be washed and dried.

Tablets

Tablets may be prepared by conventional procedures so that the dosage unit is 100 milligrams of active ingredient, 20 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

25 Injectable

A parenteral composition suitable for administration by injection may be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution should be made isotonic with sodium chloride and 30 sterilized.

Suspension

An aqueous suspension can be prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be

about 0.1 to 100 milligrams of the compound of Formula I and about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an 5 amount of about 5 to 10 milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams per dosage unit.

Where the compounds of Formula I are administered in combination with an anti-platelet agent, by way of general 10 guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of Formula I and about 50 to 150 milligrams of the anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of Formula I and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient 15 body weight.

Where the compounds of Formula I are administered in combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of Formula I, per kilogram of patient body weight and, in the case of the 20 thrombolytic agents, the usual dosage of the thrombolytic agent when administered alone may be reduced by about 70-80% when administered with a compound of Formula I.

Where two or more of the foregoing second therapeutic agents are administered with the compound of Formula I, 25 generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are 30 combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active 35 ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating

one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one 5 of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active 10 ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained 15 and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an 20 additional barrier to interaction with the other component.

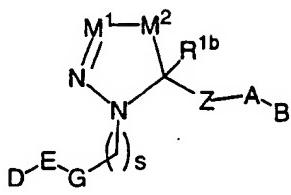
These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the 25 same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the 30 scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

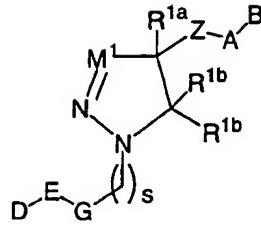
WHAT IS CLAIMED IS:

1. A compound of formula I:

5



I



II

or a stereoisomer or pharmaceutically acceptable salt thereof,  
wherein;

10 M¹ is N or CR¹c;

M² is NR¹a or CR¹aR¹a, provided that only one of M¹ and M² is a  
N atom;

15 D is selected from C(=NR⁸)NR⁷R⁹, NHC(=NR⁸)NR⁷R⁹, NR⁸CH(=NR⁷),  
C(O)NR⁷R⁸, and CR⁸R⁹NR⁷R⁸;

E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl,  
pyridazinyl, and piperidinyl substituted with 1 R;

20

alternatively, D-E-G together represent pyridyl substituted  
with 1 R;

R is selected from H, Cl, F, Br, I, (CH₂)ₜOR³, C₁-₄ alkyl,  
25 OCF₃, CF₃, C(O)NR⁷R⁸, and (CR⁸R⁹)ₜNR⁷R⁸;

G is selected from NHCH₂, OCH₂, and SCH₂, provided that when s  
is 0, then G is absent;

30 Z is selected from a C₁-₄ alkylene, (CH₂)ₜO(CH₂)ₜ,  
(CH₂)ₜNR³(CH₂)ₜ, (CH₂)ₜC(O)(CH₂)ₜ, (CH₂)ₜC(O)O(CH₂)ₜ,  
(CH₂)ₜOC(O)(CH₂)ₜ, (CH₂)ₜC(O)NR³(CH₂)ₜ,  
(CH₂)ₜNR³C(O)(CH₂)ₜ, (CH₂)ₜOC(O)O(CH₂)ₜ,  
(CH₂)ₜOC(O)NR³(CH₂)ₜ, (CH₂)ₜNR³C(O)O(CH₂)ₜ,

$(CH_2)_rNR^3C(O)NR^3(CH_2)_r$ ,  $(CH_2)_rS(O)_p(CH_2)_r$ ,  
 $(CH_2)_rSO_2NR^3(CH_2)_r$ ,  $(CH_2)_rNR^3SO_2(CH_2)_r$ , and  
 $(CH_2)_rNR^3SO_2NR^3(CH_2)_r$ , provided that Z does not form a N-  
N, N-O, N-S, NCH<sub>2</sub>N, NCH<sub>2</sub>O, or NCH<sub>2</sub>S bond with group A;

5

R<sup>1a</sup> and R<sup>1b</sup> are, at each occurrence, independently selected from H, -(CH<sub>2</sub>)<sub>r</sub>-R<sup>1'</sup>, NCH<sub>2</sub>R<sup>1''</sup>, OCH<sub>2</sub>R<sup>1''</sup>, SCH<sub>2</sub>R<sup>1''</sup>,  
N(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>t</sub>R<sup>1'</sup>, O(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>t</sub>R<sup>1'</sup>, and S(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>t</sub>R<sup>1'</sup>;

10 R<sup>1c</sup> is selected from H, -(CH<sub>2</sub>)<sub>q</sub>-R<sup>1'</sup>, C<sub>1-3</sub> alkyl, C(O)R<sup>2c</sup>,  
(CF<sub>2</sub>)<sub>r</sub>CO<sub>2</sub>R<sup>2c</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>, C<sub>3-6</sub> carbocyclic residue substituted with 0-2 R<sup>4</sup>, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R<sup>4</sup>;

15

R<sup>1'</sup> is selected from H, C<sub>1-3</sub> alkyl, halo, (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>, OR<sup>2</sup>, NR<sup>2</sup>R<sup>2a</sup>, C(O)R<sup>2c</sup>, OC(O)R<sup>2</sup>, (CF<sub>2</sub>)<sub>r</sub>CO<sub>2</sub>R<sup>2c</sup>, S(O)<sub>p</sub>R<sup>2b</sup>, NR<sup>2</sup>(CH<sub>2</sub>)<sub>r</sub>OR<sup>2</sup>, NR<sup>2</sup>C(O)R<sup>2b</sup>, NR<sup>2</sup>C(O)NHR<sup>2b</sup>, NR<sup>2</sup>C(O)<sub>2</sub>R<sup>2a</sup>, OC(O)NR<sup>2b</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>SO<sub>2</sub>R<sup>2b</sup>, C<sub>3-6</sub>

20 carbocyclic residue substituted with 0-2 R<sup>4</sup>, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R<sup>4</sup>;

25 R<sup>1''</sup> is selected from H, C(O)R<sup>2b</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>, S(O)R<sup>2b</sup>, S(O)<sub>2</sub>R<sup>2b</sup>, and SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>;

30 R<sup>2</sup>, at each occurrence, is selected from H, CF<sub>3</sub>, C<sub>1-6</sub> alkyl, benzyl, C<sub>3-6</sub> carbocyclic residue substituted with 0-2 R<sup>4b</sup>, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R<sup>4b</sup>;

35 R<sup>2a</sup>, at each occurrence, is selected from H, CF<sub>3</sub>, C<sub>1-6</sub> alkyl, benzyl, C<sub>3-6</sub> carbocyclic residue substituted with 0-2 R<sup>4b</sup>, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R<sup>4b</sup>;

R<sup>2b</sup>, at each occurrence, is selected from CF<sub>3</sub>, C<sub>1-4</sub> alkoxy, C<sub>1-6</sub> alkyl, benzyl, C<sub>3-6</sub> carbocyclic residue substituted with 0-2 R<sup>4b</sup>, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R<sup>4b</sup>;

5 R<sup>2c</sup>, at each occurrence, is selected from CF<sub>3</sub>, OH, C<sub>1-4</sub> alkoxy, C<sub>1-6</sub> alkyl, benzyl, C<sub>3-6</sub> carbocyclic residue substituted with 0-2 R<sup>4b</sup>, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R<sup>4b</sup>;

10 alternatively, R<sup>2</sup> and R<sup>2a</sup> combine to form a 5 or 6 membered 15 saturated, partially saturated or unsaturated ring substituted with 0-2 R<sup>4b</sup> which contains from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

20 R<sup>3</sup>, at each occurrence, is selected from H, C<sub>1-4</sub> alkyl, and phenyl;

25 R<sup>3a</sup>, at each occurrence, is selected from H, C<sub>1-4</sub> alkyl, and phenyl;

A is selected from:  
C<sub>3-10</sub> carbocyclic residue substituted with 0-2 R<sup>4</sup>, and  
5-10 membered heterocyclic system containing from 1-4  
heteroatoms selected from the group consisting of N, O, and S  
30 substituted with 0-2 R<sup>4</sup>;

B is selected from:  
X-Y, NR<sup>2</sup>R<sup>2a</sup>, C(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>C(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>,  
C<sub>3-10</sub> carbocyclic residue substituted with 0-2 R<sup>4a</sup>, and  
35 5-10 membered heterocyclic system containing from 1-4  
heteroatoms selected from the group consisting of N, O, and S  
substituted with 0-2 R<sup>4a</sup>;

X is selected from C<sub>1-4</sub> alkylene, -CR<sup>2</sup>(CR<sup>2</sup>R<sup>2b</sup>)(CH<sub>2</sub>)<sub>t</sub>-, -C(O)-, -C(=NR)-, -CR<sup>2</sup>(NR<sup>1</sup>R<sup>2</sup>)-, -CR<sup>2</sup>(OR<sup>2</sup>)-, -CR<sup>2</sup>(SR<sup>2</sup>)-, -C(O)CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>C(O), -S(O)<sub>p</sub>-, -S(O)<sub>p</sub>CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>S(O)<sub>p</sub>-, -S(O)<sub>2</sub>NR<sup>2</sup>-, -NR<sup>2</sup>S(O)<sub>2</sub>-, -NR<sup>2</sup>S(O)<sub>2</sub>CR<sup>2</sup>R<sup>2a</sup>-, 5 -CR<sup>2</sup>R<sup>2a</sup>S(O)<sub>2</sub>NR<sup>2</sup>-, -NR<sup>2</sup>S(O)<sub>2</sub>NR<sup>2</sup>-, -C(O)NR<sup>2</sup>-, -NR<sup>2</sup>C(O)-, -C(O)NR<sup>2</sup>CR<sup>2</sup>R<sup>2a</sup>-, -NR<sup>2</sup>C(O)CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>C(O)NR<sup>2</sup>-, -CR<sup>2</sup>R<sup>2a</sup>NR<sup>2</sup>C(O)-, -NR<sup>2</sup>C(O)O-, -OC(O)NR<sup>2</sup>-, -NR<sup>2</sup>C(O)NR<sup>2</sup>-, -NR<sup>2</sup>-, -NR<sup>2</sup>CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>NR<sup>2</sup>-, O, -CR<sup>2</sup>R<sup>2a</sup>O-, and -OCR<sup>2</sup>R<sup>2a</sup>-,

10

Y is selected from:

(CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, provided that X-Y do not form a N-N, O-N, or S-N bond,

15 C<sub>3-10</sub> carbocyclic residue substituted with 0-2 R<sup>4a</sup>, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R<sup>4a</sup>;

20 R<sup>4</sup>, at each occurrence, is selected from =O, (CH<sub>2</sub>)<sub>r</sub>OR<sup>2</sup>, halo, C<sub>1-4</sub> alkyl, -CN, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, (CH<sub>2</sub>)<sub>r</sub>C(O)R<sup>2b</sup>, NR<sup>2</sup>C(O)R<sup>2b</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>C(O)NR<sup>2</sup>R<sup>2a</sup>, CH(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>, NHC(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>SO<sub>2</sub>-C<sub>1-4</sub> alkyl, NR<sup>2</sup>SO<sub>2</sub>R<sup>5</sup>, S(O)<sub>p</sub>R<sup>5</sup>, (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>, NCH<sub>2</sub>R<sup>1</sup>′, OCH<sub>2</sub>R<sup>1</sup>′, SCH<sub>2</sub>R<sup>1</sup>′, N(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>t</sub>R<sup>1</sup>′, O(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>t</sub>R<sup>1</sup>′, and 25 S(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>t</sub>R<sup>1</sup>′,

alternatively, one R<sup>4</sup> is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

30

R<sup>4a</sup>, at each occurrence, is selected from =O, (CH<sub>2</sub>)<sub>r</sub>OR<sup>2</sup>, halo, C<sub>1-4</sub> alkyl, -CN, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, (CH<sub>2</sub>)<sub>r</sub>C(O)R<sup>2b</sup>, NR<sup>2</sup>C(O)R<sup>2b</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>C(O)NR<sup>2</sup>R<sup>2a</sup>, CH(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>, NHC(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>SO<sub>2</sub>-C<sub>1-4</sub> alkyl, NR<sup>2</sup>SO<sub>2</sub>R<sup>5</sup>, S(O)<sub>p</sub>R<sup>5</sup>, and (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>;

alternatively, one R<sup>4a</sup> is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-1 R<sup>5</sup>;

5 R<sup>4b</sup>, at each occurrence, is selected from =O, (CH<sub>2</sub>)<sub>r</sub>OR<sup>3</sup>, halo, C<sub>1-4</sub> alkyl, -CN, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>r</sub>NR<sup>3</sup>R<sup>3a</sup>, (CH<sub>2</sub>)<sub>r</sub>C(O)R<sup>3</sup>, NR<sup>3</sup>C(O)R<sup>3a</sup>, C(O)NR<sup>3</sup>R<sup>3a</sup>, NR<sup>3</sup>C(O)NR<sup>3</sup>R<sup>3a</sup>, CH(=NR<sup>3</sup>)NR<sup>3</sup>R<sup>3a</sup>, NH<sup>3</sup>C(=NR<sup>3</sup>)NR<sup>3</sup>R<sup>3a</sup>, SO<sub>2</sub>NR<sup>3</sup>R<sup>3a</sup>, NR<sup>3</sup>SO<sub>2</sub>NR<sup>3</sup>R<sup>3a</sup>, NR<sup>3</sup>SO<sub>2</sub>-C<sub>1-4</sub> alkyl, NR<sup>3</sup>SO<sub>2</sub>CF<sub>3</sub>, NR<sup>3</sup>SO<sub>2</sub>-phenyl, S(O)<sub>p</sub>CF<sub>3</sub>, S(O)<sub>p</sub>-C<sub>1-4</sub> alkyl, S(O)<sub>p</sub>-phenyl, and (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>;

10 R<sup>5</sup>, at each occurrence, is selected from CF<sub>3</sub>, C<sub>1-6</sub> alkyl, phenyl substituted with 0-2 R<sup>6</sup>, and benzyl substituted with 0-2 R<sup>6</sup>;

15 R<sup>6</sup>, at each occurrence, is selected from H, OH, (CH<sub>2</sub>)<sub>r</sub>OR<sup>2</sup>, halo, C<sub>1-4</sub> alkyl, CN, NO<sub>2</sub>, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, (CH<sub>2</sub>)<sub>r</sub>C(O)R<sup>2b</sup>, NR<sup>2</sup>C(O)R<sup>2b</sup>, NR<sup>2</sup>C(O)NR<sup>2</sup>R<sup>2a</sup>, CH(=NH)NH<sub>2</sub>, NHC(=NH)NH<sub>2</sub>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, NR<sup>2</sup>SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, and NR<sup>2</sup>SO<sub>2</sub>C<sub>1-4</sub> alkyl;

20 R<sup>7</sup>, at each occurrence, is selected from H, OH, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy, C<sub>1-4</sub> alkoxy carbonyl, (CH<sub>2</sub>)<sub>n</sub>-phenyl, C<sub>6-10</sub> aryloxy, C<sub>6-10</sub> aryloxycarbonyl, C<sub>6-10</sub> arylmethylcarbonyl, C<sub>1-4</sub> alkylcarbonyloxy C<sub>1-4</sub> alkoxy carbonyl, C<sub>6-10</sub> arylcarbonyloxy C<sub>1-4</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C<sub>1-4</sub> alkoxy carbonyl;

25 R<sup>8</sup>, at each occurrence, is selected from H, C<sub>1-6</sub> alkyl and (CH<sub>2</sub>)<sub>n</sub>-phenyl;

30 alternatively, R<sup>7</sup> and R<sup>8</sup> combine to form a 5 or 6 membered saturated, ring which contains from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

35 R<sup>9</sup>, at each occurrence, is selected from H, C<sub>1-6</sub> alkyl and (CH<sub>2</sub>)<sub>n</sub>-phenyl;

n, at each occurrence, is selected from 0, 1, 2, and 3;

m, at each occurrence, is selected from 0, 1, and 2;

5

p, at each occurrence, is selected from 0, 1, and 2;

q, at each occurrence is selected from 1 and 2;

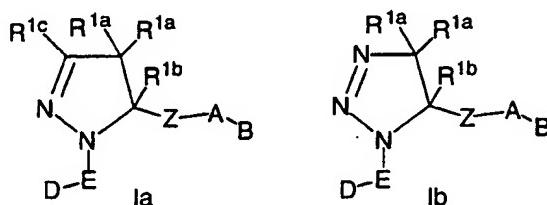
10 r, at each occurrence, is selected from 0, 1, 2, and 3;

s, at each occurrence, is selected from 0, 1, and 2; and,

t, at each occurrence, is selected from 0 and 1.

15

2. A compound according to Claim 1, wherein the compound is of formula Ia or Ib:



20

wherein;

Z is selected from a CH<sub>2</sub>O, OCH<sub>2</sub>, CH<sub>2</sub>NH, NHCH<sub>2</sub>, C(O), CH<sub>2</sub>C(O),  
C(O)CH<sub>2</sub>, NHC(O), C(O)NH, CH<sub>2</sub>S(O)<sub>2</sub>, S(O)<sub>2</sub>(CH<sub>2</sub>), SO<sub>2</sub>NH, and

25

NHSO<sub>2</sub>, provided that Z does not form a N-N, N-O, NCH<sub>2</sub>N,  
or NCH<sub>2</sub>O bond with group A;

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R<sup>4</sup>;

30

phenyl, piperidinyl, piperazinyl, pyridyl,  
pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl,  
pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl,  
isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl,  
thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,

1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,  
1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl,  
1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl,  
1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl,  
5 benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl,  
benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl,  
benzisothiazolyl, and isoindazolyl;

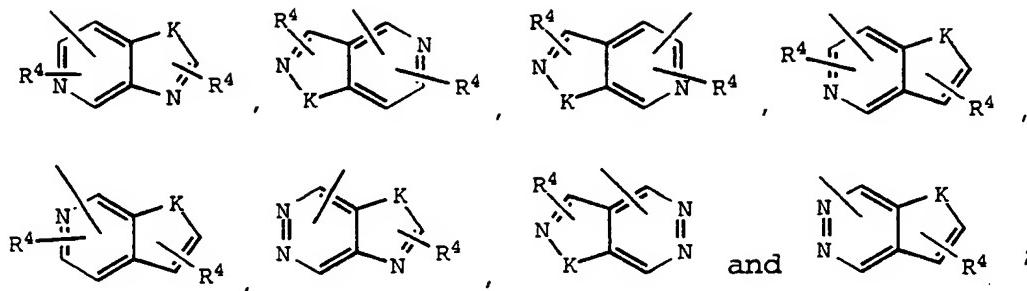
B is selected from: Y, X-Y, NR<sup>2</sup>R<sup>2a</sup>, C(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>, and  
10 NR<sup>2</sup>C(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>;

X is selected from C<sub>1-4</sub> alkylene, -C(O)-, -C(=NR)-,  
-CR<sup>2</sup>(NR<sup>2</sup>R<sup>2a</sup>)-, -C(O)CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>C(O), -C(O)NR<sup>2</sup>-,  
-NR<sup>2</sup>C(O)-, -C(O)NR<sup>2</sup>CR<sup>2</sup>R<sup>2a</sup>-, -NR<sup>2</sup>C(O)CR<sup>2</sup>R<sup>2a</sup>-,  
15 -CR<sup>2</sup>R<sup>2a</sup>C(O)NR<sup>2</sup>-, -CR<sup>2</sup>R<sup>2a</sup>NR<sup>2</sup>C(O)-, -NR<sup>2</sup>C(O)NR<sup>2</sup>-, -NR<sup>2</sup>-,  
-NR<sup>2</sup>CR<sup>2</sup>R<sup>2a</sup>-, -CR<sup>2</sup>R<sup>2a</sup>NR<sup>2</sup>-, O, -CR<sup>2</sup>R<sup>2a</sup>O-, and -OCR<sup>2</sup>R<sup>2a</sup>-;

Y is NR<sup>2</sup>R<sup>2a</sup>, provided that X-Y do not form a N-N or O-N bond;  
20 alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R<sup>4a</sup>;

cyclopropyl, cyclopentyl, cyclohexyl, phenyl,  
piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl,  
25 morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl,  
oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl,  
isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl,  
thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,  
1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,  
30 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl,  
1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl,  
1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl,  
benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl,  
benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl,  
35 benzisothiazolyl, and isoindazolyl;

alternatively, Y is selected from the following bicyclic heteroaryl ring systems:



K is selected from O, S, NH, and N.

5

3. A compound according to Claim 2, wherein;

Z is selected from a C(O), CH<sub>2</sub>C(O), C(O)CH<sub>2</sub>, NHC(O), C(O)NH,

10 C(O)N(CH<sub>3</sub>), CH<sub>2</sub>S(O)<sub>2</sub>, S(O)<sub>2</sub>(CH<sub>2</sub>), SO<sub>2</sub>NH, and NHSO<sub>2</sub>,

provided that Z does not form a N-N or NCH<sub>2</sub>N bond with  
group A.

4. A compound according to Claim 3, wherein;

15

E is phenyl substituted with R or 2-pyridyl substituted with  
R;

D is selected from C(O)NH<sub>2</sub>, C(=NH)NH<sub>2</sub>, CH<sub>2</sub>NH<sub>2</sub>, CH<sub>2</sub>NHCH<sub>3</sub>,

20 CH(CH<sub>3</sub>)NH<sub>2</sub>, and C(CH<sub>3</sub>)<sub>2</sub>NH<sub>2</sub>; and,

R is selected from H, OCH<sub>3</sub>, Cl, and F.

25

5. A compound according to Claim 4, wherein;

D-E is selected from 3-amidinophenyl, 3-aminomethylphenyl, 3-  
aminocarbonylphenyl, 3-(methylaminomethyl)phenyl, 3-(1-  
aminoethyl)phenyl, 3-(2-amino-2-propyl)phenyl, 4-chloro-  
30 3-amidinophenyl, 4-chloro-3-aminomethylphenyl, 4-chloro-  
3-(methylaminomethyl)phenyl, 4-fluoro-3-amidinophenyl, 4-  
fluoro-3-aminomethylphenyl, 4-fluoro-3-

(methylaminomethyl)phenyl, 6-amidinopyrid-2-yl, 6-aminomethylpyrid-2-yl, 6-aminocarbonylpyrid-2-yl, 6-(methylaminomethyl)pyrid-2-yl, 6-(1-aminoethyl)pyrid-2-yl, and 6-(2-amino-2-propyl)pyrid-2-yl.

5

6. A compound according to Claim 3, wherein;

Z is C(O)CH<sub>2</sub> and CONH, provided that Z does not form a N-N  
10 bond with group A;

A is selected from phenyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R<sup>4</sup>; and,

15 B is selected from X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, and imidazolyl, and is substituted with 0-1 R<sup>4a</sup>;

R<sup>4</sup>, at each occurrence, is selected from OH, (CH<sub>2</sub>)<sub>r</sub>OR<sup>2</sup>, halo,  
20 C<sub>1-4</sub> alkyl, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, and (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>;

R<sup>4a</sup> is selected from C<sub>1-4</sub> alkyl, CF<sub>3</sub>, S(O)<sub>p</sub>R<sup>5</sup>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, and 1-CF<sub>3</sub>-tetrazol-2-yl;

25 R<sup>5</sup>, at each occurrence, is selected from CF<sub>3</sub>, C<sub>1-6</sub> alkyl, phenyl, and benzyl;

X is CH<sub>2</sub> or C(O); and,

30 Y is selected from pyrrolidino and morpholino.

7. A compound according to Claim 6, wherein;

35 A is selected from the group: phenyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,

B is selected from the group: 2-CF<sub>3</sub>-phenyl, 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 2-(dimethylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 4-morpholino, 2-(1'-CF<sub>3</sub>-tetrazol-2-yl)phenyl, 4-morpholinocarbonyl, 2-methyl-1-imidazolyl, 5-methyl-1-imidazolyl, 2-methylsulfonyl-1-imidazolyl and, 5-methyl-1,2,3-triazolyl.

10

8. A compound according to Claim 3, wherein;

E is phenyl substituted with R or 2-pyridyl substituted with R;

15

D is selected from C(O)NH<sub>2</sub>, C(=NH)NH<sub>2</sub>, CH<sub>2</sub>NH<sub>2</sub>, CH<sub>2</sub>NHCH<sub>3</sub>, CH(CH<sub>3</sub>)NH<sub>2</sub>, and C(CH<sub>3</sub>)<sub>2</sub>NH<sub>2</sub>; and,

R is selected from H, OCH<sub>3</sub>, Cl, and F;

20

Z is C(O)CH<sub>2</sub> and CONH, provided that Z does not form a N-N bond with group A;

25

A is selected from phenyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R<sup>4</sup>; and,

B is selected from X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, and imidazolyl, and is substituted with 0-1 R<sup>4a</sup>;

30

R<sup>4</sup>, at each occurrence, is selected from OH, (CH<sub>2</sub>)<sub>r</sub>OR<sup>2</sup>, halo, C<sub>1-4</sub> alkyl, (CH<sub>2</sub>)<sub>r</sub>NR<sup>2</sup>R<sup>2a</sup>, and (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>;

35

R<sup>4a</sup> is selected from C<sub>1-4</sub> alkyl, CF<sub>3</sub>, S(O)<sub>p</sub>R<sup>5</sup>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, and 1-CF<sub>3</sub>-tetrazol-2-yl;

R<sup>5</sup>, at each occurrence, is selected from CF<sub>3</sub>, C<sub>1-6</sub> alkyl, phenyl, and benzyl;

X is CH<sub>2</sub> or C(O); and,

Y is selected from pyrrolidino and morpholino.

5

9. A compound according to Claim 8 wherein;

D-E is selected from 3-amidinophenyl, 3-aminomethylphenyl, 3-aminocarbonylphenyl, 3-(methylaminomethyl)phenyl, 3-(1-aminoethyl)phenyl, 3-(2-amino-2-propyl)phenyl, 4-chloro-3-amidinophenyl, 4-chloro-3-aminomethylphenyl, 4-chloro-3-(methylaminomethyl)phenyl, 4-fluoro-3-amidinophenyl, 4-fluoro-3-aminomethylphenyl, 4-fluoro-3-(methylaminomethyl)phenyl, 6-amidinopyrid-2-yl, 6-aminomethylpyrid-2-yl, 6-aminocarbonylpyrid-2-yl, 6-(methylaminomethyl)pyrid-2-yl, 6-(1-aminoethyl)pyrid-2-yl, 6-(2-amino-2-propyl)pyrid-2-yl;

20 A is selected from the group: phenyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,

25 B is selected from the group: 2-CF<sub>3</sub>-phenyl, 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 2-(dimethylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 4-morpholino, 2-(1'-CF<sub>3</sub>-tetrazol-2-yl)phenyl, 4-morpholinocarbonyl, 2-methyl-1-imidazolyl, 30 5-methyl-1-imidazolyl, 2-methylsulfonyl-1-imidazolyl and, 5-methyl-1,2,3-triazolyl.

10. A compound according to Claim 9, wherein the  
35 compound is of formula Ia.

11. A compound according to Claim 9, wherein the compound is of formula Ib.

5 12. A compound according to Claim 3, wherein;

D is selected from  $C(=NR^8)NR^7R^9$ ,  $C(O)NR^7R^8$ ,  $NR^7R^8$ , and  $CH_2NR^7R^8$ ;

10 E is phenyl substituted with R or pyridyl substituted with R;

R is selected from H, Cl, F, OR<sup>3</sup>, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, OCF<sub>3</sub>, and CF<sub>3</sub>;

15 Z is selected from C(O), CH<sub>2</sub>C(O), C(O)CH<sub>2</sub>, NHC(O), and C(O)NH, provided that Z does not form a N-N bond with group A;

R<sup>1a</sup> and R<sup>1b</sup> are, at each occurrence, independently selected from H, -(CH<sub>2</sub>)<sub>r</sub>-R<sup>1'</sup>, NCH<sub>2</sub>R<sup>1''</sup>, OCH<sub>2</sub>R<sup>1''</sup>, SCH<sub>2</sub>R<sup>1''</sup>, N(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>t</sub>R<sup>1'</sup>, O(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>t</sub>R<sup>1'</sup>, and S(CH<sub>2</sub>)<sub>2</sub>(CH<sub>2</sub>)<sub>t</sub>R<sup>1'</sup>;

20 R<sup>1c</sup> is selected from H, -(CH<sub>2</sub>)<sub>q</sub>-R<sup>1'</sup>, C<sub>1-3</sub> alkyl, C(O)R<sup>2c</sup>, (CF<sub>2</sub>)<sub>r</sub>CO<sub>2</sub>R<sup>2c</sup>, and C(O)NR<sup>2</sup>R<sup>2a</sup>;

25 R<sup>1'</sup>, at each occurrence, is selected from H, C<sub>1-3</sub> alkyl, halo, (CF<sub>2</sub>)<sub>r</sub>CF<sub>3</sub>, OR<sup>2</sup>, NR<sup>2</sup>R<sup>2a</sup>, C(O)R<sup>2c</sup>, (CF<sub>2</sub>)<sub>r</sub>CO<sub>2</sub>R<sup>2c</sup>, S(O)<sub>p</sub>R<sup>2b</sup>, NR<sup>2</sup>(CH<sub>2</sub>)<sub>r</sub>OR<sup>2</sup>, NR<sup>2</sup>C(O)R<sup>2b</sup>, NR<sup>2</sup>C(O)<sub>2</sub>R<sup>2b</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, and NR<sup>2</sup>SO<sub>2</sub>R<sup>2b</sup>;

30 A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R<sup>4</sup>; phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, and imidazolyl;

35 B is selected from: Y, X-Y, NR<sup>2</sup>R<sup>2a</sup>, C(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>, and NR<sup>2</sup>C(=NR<sup>2</sup>)NR<sup>2</sup>R<sup>2a</sup>;

X is selected from  $\text{CH}_2$ ,  $-\text{CR}^2(\text{CR}^2\text{R}^{2b})(\text{CH}_2)_t-$ ,  $-\text{C(O)}-$ ,  $-\text{C(=NR)}-$ ,  $-\text{CH(NR}^2\text{R}^{2a})-$ ,  $-\text{C(O)NR}^2-$ ,  $-\text{NR}^2\text{C(O)}-$ ,  $-\text{NR}^2\text{C(O)NR}^2-$ ,  $-\text{NR}^2-$ , and O;

5 Y is  $\text{NR}^2\text{R}^{2a}$ , provided that X-Y do not form a N-N or O-N bond;

alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R<sup>4a</sup>:

10 phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 15 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, and 1,3,4-triazolyl;

20 R<sup>4</sup>, at each occurrence, is selected from =O, OH, Cl, F, C<sub>1-4</sub> alkyl,  $(\text{CH}_2)_r\text{NR}^2\text{R}^{2a}$ ,  $(\text{CH}_2)_r\text{C(O)R}^{2b}$ ,  $\text{NR}^2\text{C(O)R}^{2b}$ ,  $\text{C(O)NR}^2\text{R}^{2a}$ ,  $\text{CH(=NH)NH}_2$ ,  $\text{NHC(=NH)NH}_2$ ,  $\text{SO}_2\text{NR}^2\text{R}^{2a}$ ,  $\text{NR}^2\text{SO}_2\text{-C}_{1-4}$  alkyl,  $\text{NR}^2\text{SO}_2\text{R}^5$ ,  $\text{S(O)}_p\text{R}^5$ , and  $(\text{CF}_2)_r\text{CF}_3$ ;

25 R<sup>4a</sup>, at each occurrence, is selected from =O, OH, Cl, F, C<sub>1-4</sub> alkyl,  $(\text{CH}_2)_r\text{NR}^2\text{R}^{2a}$ ,  $(\text{CH}_2)_r\text{C(O)R}^{2b}$ ,  $\text{NR}^2\text{C(O)R}^{2b}$ ,  $\text{C(O)NR}^2\text{R}^{2a}$ ,  $\text{CH(=NH)NH}_2$ ,  $\text{NHC(=NH)NH}_2$ ,  $\text{SO}_2\text{NR}^2\text{R}^{2a}$ ,  $\text{NR}^2\text{SO}_2\text{-C}_{1-4}$  alkyl,  $\text{NR}^2\text{SO}_2\text{R}^5$ ,  $\text{S(O)}_p\text{R}^5$ ,  $(\text{CF}_2)_r\text{CF}_3$ , and 1-CF<sub>3</sub>-tetrazol-2-yl;

30 R<sup>5</sup>, at each occurrence, is selected from CF<sub>3</sub>, C<sub>1-6</sub> alkyl, phenyl substituted with 0-2 R<sup>6</sup>, and benzyl substituted with 0-2 R<sup>6</sup>;

35 R<sup>6</sup>, at each occurrence, is selected from H, =O, OH, OR<sup>2</sup>, Cl, F, CH<sub>3</sub>, CN, NO<sub>2</sub>,  $(\text{CH}_2)_r\text{NR}^2\text{R}^{2a}$ ,  $(\text{CH}_2)_r\text{C(O)R}^{2b}$ ,  $\text{NR}^2\text{C(O)R}^{2b}$ ,  $\text{CH(=NH)NH}_2$ ,  $\text{NHC(=NH)NH}_2$ , and  $\text{SO}_2\text{NR}^2\text{R}^{2a}$ ;

R<sup>7</sup>, at each occurrence, is selected from H, OH, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkylcarbonyl, C<sub>1-6</sub> alkoxy, C<sub>1-4</sub> alkoxycarbonyl, benzyl, C<sub>6-10</sub> aryloxy, C<sub>6-10</sub> aryloxycarbonyl, C<sub>6-10</sub> arylmethylcarbonyl, C<sub>1-4</sub> alkylcarbonyloxy C<sub>1-4</sub> alkoxycarbonyl, C<sub>6-10</sub> arylcarbonyloxy C<sub>1-4</sub> alkoxycarbonyl, C<sub>1-6</sub> alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C<sub>1-4</sub> alkoxycarbonyl;

R<sup>8</sup>, at each occurrence, is selected from H, C<sub>1-6</sub> alkyl and benzyl; and

alternatively, R<sup>7</sup> and R<sup>8</sup> combine to form a morpholino group; and,

R<sup>9</sup>, at each occurrence, is selected from H, C<sub>1-6</sub> alkyl and benzyl.

13. A compound according to Claim 12, wherein;  
E is phenyl substituted with R or 2-pyridyl substituted with R;

R is selected from H, Cl, F, OCH<sub>3</sub>, CH<sub>3</sub>, OCF<sub>3</sub>, and CF<sub>3</sub>;

Z is selected from a C(O)CH<sub>2</sub> and C(O)NH, provided that Z does not form a N-N bond with group A;

R<sup>1a</sup>, at each occurrence, is selected from H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, Cl, F, CF<sub>3</sub>, OCH<sub>3</sub>, NR<sup>2</sup>R<sup>2a</sup>, S(O)<sub>p</sub>R<sup>2b</sup>, CH<sub>2</sub>S(O)<sub>p</sub>R<sup>2b</sup>, CH<sub>2</sub>NR<sup>2</sup>S(O)<sub>p</sub>R<sup>2b</sup>, C(O)R<sup>2c</sup>, CH<sub>2</sub>C(O)R<sup>2c</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>, and SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>;

R<sup>1b</sup> is selected from H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, Cl, F, CF<sub>3</sub>, OCH<sub>3</sub>, NR<sup>2</sup>R<sup>2a</sup>, S(O)<sub>p</sub>R<sup>2b</sup>, CH<sub>2</sub>S(O)<sub>p</sub>R<sup>2b</sup>, CH<sub>2</sub>NR<sup>2</sup>S(O)<sub>p</sub>R<sup>2b</sup>, C(O)R<sup>2c</sup>, CH<sub>2</sub>C(O)R<sup>2c</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>, and SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>;

$R^{1c}$  is selected from H,  $CH_3$ ,  $CH_2CH_3$ ,  $CF_3$ ,  $CH_2S(O)_pR^{2b}$ ,  
 $CH_2NR^2S(O)_pR^{2b}$ ,  $C(O)R^{2c}$ ,  $CH_2C(O)R^{2c}$ , and  $C(O)NR^2R^{2a}$ ;

5 A is selected from one of the following carbocyclic and  
heterocyclic systems which are substituted with 0-2  $R^4$ ;  
phenyl, pyridyl, pyrimidyl, furanyl, thiophenyl,  
pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl,  
pyrazolyl, and imidazolyl;

10 B is selected from: Y and X-Y;

X is selected from  $CH_2$ ,  $-CR^2(CR^2R^{2b})-$ ,  $-C(O)-$ ,  $-C(=NR)-$ ,  
 $-CH(NR^2R^{2a})-$ ,  $-C(O)NR^2-$ ,  $-NR^2C(O)-$ ,  $-NR^2C(O)NR^2-$ ,  $-NR^2-$ ,  
and O;

15 15 Y is  $NR^2R^{2a}$ , provided that X-Y do not form a N-N or O-N bond;

alternatively, Y is selected from one of the following  
carbocyclic and heterocyclic systems which are  
20 substituted with 0-2  $R^{4a}$ ;  
phenyl, piperidinyl, piperazinyl, pyridyl,  
pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl,  
pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl,  
thiazolyl, isothiazolyl, pyrazolyl, imidazolyl,  
25 oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,  
1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,  
1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl,  
1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl,  
1,2,4-triazolyl, 1,2,5-triazolyl, and 1,3,4-triazolyl;

30  $R^2$ , at each occurrence, is selected from H,  $CF_3$ ,  $CH_3$ , benzyl,  
and phenyl;

35  $R^{2a}$ , at each occurrence, is selected from H,  $CF_3$ ,  $CH_3$ , benzyl,  
and phenyl;

$R^{2b}$ , at each occurrence, is selected from  $CF_3$ ,  $OCH_3$ ,  $CH_3$ ,  
benzyl, and phenyl;

R<sup>2c</sup>, at each occurrence, is selected from CF<sub>3</sub>, OH, OCH<sub>3</sub>, CH<sub>3</sub>, benzyl, and phenyl;

5 alternatively, R<sup>2</sup> and R<sup>2a</sup> combine to form a 5 or 6 membered saturated, partially unsaturated, or unsaturated ring which contains from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

10 R<sup>3</sup>, at each occurrence, is selected from H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, and phenyl;

R<sup>3a</sup>, at each occurrence, is selected from H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, and phenyl;

15 R<sup>4</sup>, at each occurrence, is selected from OH, Cl, F, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, NR<sup>2</sup>R<sup>2a</sup>, CH<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, C(O)R<sup>2b</sup>, NR<sup>2</sup>C(O)R<sup>2b</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>, and CF<sub>3</sub>;

20 R<sup>4a</sup>, at each occurrence, is selected from OH, Cl, F, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, NR<sup>2</sup>R<sup>2a</sup>, CH<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, C(O)R<sup>2b</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, S(O)<sub>p</sub>R<sup>5</sup>, CF<sub>3</sub>, and 1-CF<sub>3</sub>-tetrazol-2-yl;

25 R<sup>5</sup>, at each occurrence, is selected from CF<sub>3</sub>, C<sub>1-6</sub> alkyl, phenyl substituted with 0-2 R<sup>6</sup>, and benzyl substituted with 1 R<sup>6</sup>;

R<sup>6</sup>, at each occurrence, is selected from H, OH, OCH<sub>3</sub>, Cl, F, CH<sub>3</sub>, CN, NO<sub>2</sub>, NR<sup>2</sup>R<sup>2a</sup>, CH<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, and SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>;

30 R<sup>7</sup>, at each occurrence, is selected from H, OH, C<sub>1-3</sub> alkyl, C<sub>1-3</sub> alkylcarbonyl, C<sub>1-3</sub> alkoxy, C<sub>1-4</sub> alkoxycarbonyl, benzyl, phenoxy, phenoxy carbonyl, benzyl carbonyl, C<sub>1-4</sub> alkylcarbonyloxy, C<sub>1-4</sub> alkoxy carbonyl, phenyl carbonyloxy, C<sub>1-4</sub> alkoxy carbonyl, C<sub>1-6</sub> alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C<sub>1-4</sub> alkoxy carbonyl;

R<sup>8</sup>, at each occurrence, is selected from H, CH<sub>3</sub>, and benzyl;  
and,

alternatively, R<sup>7</sup> and R<sup>8</sup> combine to form a morpholino group;

5

R<sup>9</sup>, at each occurrence, is selected from H, CH<sub>3</sub>, and benzyl.

14. A compound according to Claim 13, wherein;

10

R<sup>1a</sup>, at each occurrence, is selected from H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, Cl,  
F, CF<sub>3</sub>, OCH<sub>3</sub>, NR<sup>2</sup>R<sup>2a</sup>, S(O)<sub>p</sub>R<sup>2b</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>, CH<sub>2</sub>S(O)<sub>p</sub>R<sup>2b</sup>,  
CH<sub>2</sub>NR<sup>2</sup>S(O)<sub>p</sub>R<sup>2b</sup>, C(O)R<sup>2c</sup>, CH<sub>2</sub>C(O)R<sup>2c</sup>, and SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>;

15 R<sup>1b</sup> is selected from H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, Cl, F, CF<sub>3</sub>, OCH<sub>3</sub>, NR<sup>2</sup>R<sup>2a</sup>,  
S(O)<sub>p</sub>R<sup>2b</sup>, C(O)NR<sup>2</sup>R<sup>2a</sup>, CH<sub>2</sub>S(O)<sub>p</sub>R<sup>2b</sup>, CH<sub>2</sub>NR<sup>2</sup>S(O)<sub>p</sub>R<sup>2b</sup>, C(O)R<sup>2b</sup>,  
CH<sub>2</sub>C(O)R<sup>2b</sup>, and SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>;

20 R<sup>1c</sup> is selected from H, CH<sub>3</sub>, CH<sub>2</sub>CH<sub>3</sub>, CF<sub>3</sub>, C(O)NR<sup>2</sup>R<sup>2a</sup>,  
CH<sub>2</sub>S(O)<sub>p</sub>R<sup>2b</sup>, CH<sub>2</sub>NR<sup>2</sup>S(O)<sub>p</sub>R<sup>2b</sup>, C(O)R<sup>2b</sup>, and CH<sub>2</sub>C(O)R<sup>2b</sup>;

A is selected from one of the following carbocyclic and  
heterocyclic systems which are substituted with 0-2 R<sup>4</sup>;  
phenyl, pyridyl, and pyrimidyl;

25

B is selected from: Y and X-Y;

X is selected from -C(O)- and O;

30 Y is NR<sup>2</sup>R<sup>2a</sup>, provided that X-Y do not form a O-N bond;

alternatively, Y is selected from one of the following  
carbocyclic and heterocyclic systems which are  
substituted with 0-2 R<sup>4a</sup>;

35 phenyl, piperazinyl, pyridyl, pyrimidyl,  
morpholinyl, pyrrolidinyl, imidazolyl, and 1,2,3-  
triazolyl;

R<sup>2</sup>, at each occurrence, is selected from H, CF<sub>3</sub>, CH<sub>3</sub>, benzyl, and phenyl;

5 R<sup>2a</sup>, at each occurrence, is selected from H, CF<sub>3</sub>, CH<sub>3</sub>, benzyl, and phenyl;

R<sup>2b</sup>, at each occurrence, is selected from CF<sub>3</sub>, OCH<sub>3</sub>, CH<sub>3</sub>, benzyl, and phenyl;

10 R<sup>2c</sup>, at each occurrence, is selected from CF<sub>3</sub>, OH, OCH<sub>3</sub>, CH<sub>3</sub>, benzyl, and phenyl;

alternatively, R<sup>2</sup> and R<sup>2a</sup> combine to form a ring system selected from pyrrolidinyl, piperazinyl and morpholino;

15 R<sup>4</sup>, at each occurrence, is selected from Cl, F, CH<sub>3</sub>, NR<sup>2</sup>R<sup>2a</sup>, and CF<sub>3</sub>;

20 R<sup>4a</sup>, at each occurrence, is selected from Cl, F, CH<sub>3</sub>, SO<sub>2</sub>NR<sup>2</sup>R<sup>2a</sup>, S(O)<sub>p</sub>R<sup>5</sup>, and CF<sub>3</sub>; and,

R<sup>5</sup>, at each occurrence, is selected from CF<sub>3</sub> and CH<sub>3</sub>.

25 15. A compound according to Claim 1, wherein the compound is selected from the group:

1-(3-amidinophenyl)-5-[(2'-methylsulfonyl-[1,1']-biphen-4-yl)-aminocarbonyl]-3-trifluoromethyl-pyrazoline; and,

30 1-(3-aminomethylphenyl)-5-[(2'-methylsulfonyl-[1,1']-biphen-4-yl)-aminocarbonyl]-3-trifluoromethyl-pyrazoline;

and pharmaceutically acceptable salts thereof.

35

16. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically

effective amount of a compound according to one of Claims 1-15 or a pharmaceutically acceptable salt thereof.

- 5        17. A method for treating or preventing a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound according to one of Claims 1-15 or a pharmaceutically acceptable salt thereof.

10

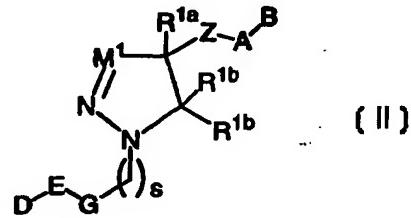
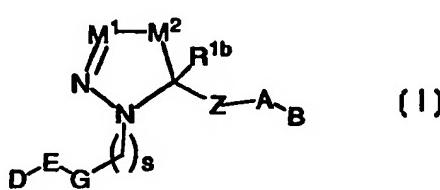


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## (54) Title: DISUBSTITUTED PYRAZOLINES AND TRIAZOLINES AS FACTOR XA INHIBITORS



## (57) Abstract

The present application describes disubstituted pyrazolines and triazolines of formulae (I) and (II), or pharmaceutically acceptable salt forms thereof, wherein one of M<sup>1</sup> and M<sup>2</sup> may be N and D may be a variety of N-containing groups, which are useful as inhibitors of factor Xa.

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/06310

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 6	C07D231/06	C07D249/10	C07D401/12	C07D403/12	A61K31/41
	A61K31/44	A61K31/505			

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 98 28269 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 2 July 1998 (1998-07-02) the whole document ---	1,15,16
P,A	WO 98 57937 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 23 December 1998 (1998-12-23) the whole document ---	1,15,16
P,A	WO 98 57951 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 23 December 1998 (1998-12-23) the whole document ---	1,15,16

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Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 September 1999

Date of mailing of the international search report

24/09/1999

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Authorized officer

Kyriakakou, G

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/06310

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 98 57934 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 23 December 1998 (1998-12-23) the whole document ---	1,15,16
A	WO 97 30971 A (THE DU PONT PHARMACEUTICAL COMPANY) 28 August 1997 (1997-08-28) page W ---	1,15,16
A	WO 97 23212 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 3 July 1997 (1997-07-03) the whole document ---	1,15,16
A	WO 95 14682 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 1 June 1995 (1995-06-01) the whole document ---	1,15,16
A	WO 95 14683 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 1 June 1995 (1995-06-01) the whole document ---	1,15,16
A	US 5 463 071 A (FRANK HIMMELSBACH ET AL.) 31 October 1995 (1995-10-31) the whole document ---	1,15,16
A	US 5 424 334 A (NORMAN A. ABOOD ET AL.) 13 June 1995 (1995-06-13) the whole document -----	1,15,16

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/06310

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 17 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see Further INFORMATION sheet PCT/ISA/210

3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: claims searched completely: 15 Claims searched incompletely 1-14, 16

In view of the large number and also the wording of the claims presently on file, which render it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of Article 84 EPC (see also Rule 29(5) EPC) to such an extent that a meaningful search is impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear (and concise), namely claim 15. Claims 1-14 and 16 have been only searched as far as specific compounds recited in the examples and closely related homologous compounds are concerned.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No

PCT/US 99/06310

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Information on patent family members

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